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Supporting Information

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Novel annulation reaction for the synthesis of morpholines, thiomorpholines and piperazines from β-heteroatom amino compounds and vinyl sulfonium salts.

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Supporting Information

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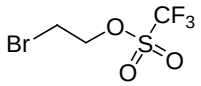
General Directions

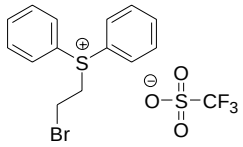
Chromatography: Flash chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) unless otherwise stated. TLC was performed on aluminium-backed silica plates (60F254, 0.2 mm). Optical rotations were measured using a Perkin-Elmer 241 MC polarimeter. $[\alpha]_D$ values are given in angular degrees per g/cm^3. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm), *J* values are given in Hz. Chemical shifts (δ_C) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak and are assigned as s, d, t, q for C, CH, CH_2, CH_3. COSY, HMBC and HMQC were used where necessary in assigning NMR spectra. Anhydrous THF, CH_2Cl_2, Et_2O and toluene were obtained from a purification column composed of activated alumina (A- 2).[1] Other anhydrous solvents were used as obtained from Aldrich.

2-Bromoethyl trifuoromethanesulfonate[2]



Trifluoromethanesulfonic anhydride (10.0 g, 35.4 mmol) was added drop-wise to a stirred solution of pyridine (2.98 mL, 36.8 mmol) in anhydrous CH_2Cl_2 (35 mL) at –20 °C under nitrogen and allowed to stir for 10 minutes. 2-Bromoethanol (4.25 g, 34.0 mmol) was added drop-wise to the reaction mixture. The cooling bath was removed and the reaction stirred for a further 10 minutes (*do not allow more than this time*) while warming. The resulting suspension was filtered, concentrated (*using a rotary evaporator, keeping the water bath temp below 20 °C*) and petroleum ether (30 mL) was added. The mixture was filtered and concentrated again under reduced pressure and finally dried under high vacuum to give the title product as a clear colorless oil (7.17 g, 82%). It was used immediately in the next step without further purification. δ_H (400 MHz; $CDCl_3$) 4.70 (2 H, t, *J* 6.5, TfO-CH_2), 3.55 (2 H, t, *J* 6.5, Br-CH_2) δ_C (100 MHz; $CDCl_3$) 74.5 (t), 26.1 (t).

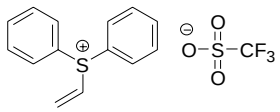
(2-Bromoethyl)diphenylsulfonium trifluoromethanesulfonate 7



A solution of 2-bromoethyl trifluoromethanesulfonate[2] (3.24 g, 12.6 mmol) in anhydrous toluene (10 mL) was treated with phenyl sulfide (2.81 g, 15.1 mmol) at RT under nitrogen with stirring. The reaction mixture was then heated at 100 °C under nitrogen for 5 h. The solution was allowed to cool to RT and diethyl ether (20 mL) was added to precipitate the product **7** which was isolated by filtration as a white powder (4.51 g, 81%) after washing with Et_2O and used in the next step without further purification.[3] mp 85–87 °C (precipitated from toluene/Et_2O) [lit.[2] 86.5–88 °C (precipitated from Et_2O/CH_2Cl_2)]; R_f (MeOH-CH_2Cl_2, 1:9) 0.20; δ_H (400 MHz; $CDCl_3$) 8.13-8.06 (4 H, m, ArH), 7.78-7.67 (6 H, m, ArH), 4.86 (2 H, t, *J* 6.5, S^+-CH_2), 3.67 (2 H, t, *J* 6.5, Br-CH_2); δ_c (100.5 MHz; $CDCl_3$) 135.3 (s), 131.9 (d), 131.2 (d), 122.9 (d), 48.3 (t), 23.8 (t).

The above reaction can also be performed using trifluorotoluene instead of toluene. On cooling white crystals form. Et_2O was added to assist mobilization. Filtration and washing with Et_2O afforded **7** as white crystals (80% yield). mp 84–87 °C (trifluorotoluene). NMR spectra were identical to when toluene was used.

Diphenylvinylsulfonium trifluoromethanesulfonate 1[2,3]



(2-Bromoethyl)diphenylsulfonium trifluoromethanesulfonate **7** (5.69 g, 12.8 mmol) was dissolved into THF / H_2O (2:1) (21 mL). $KHCO_3$ (1.54 g, 15.4 mmol) was added and the reaction mixture was stirred for 20 min at RT (do not allow more than this time). The solvent was evaporated immediately under reduced pressure (using a rotary evaporator connected to a high vacuum pump and keeping the water bath temperature below 20 °C) and then redissolved in CH_2Cl_2 (40 mL), dried over $MgSO_4$, filtered and evaporated. The residue was redissolved in CH_2Cl_2 (10 mL), loaded on a silica bed (4 cm depth and 2.5 cm diameter), the resulting band was covered with 1 cm sand, eluted

with CH_2Cl_2 (400 mL), followed by 10% MeOH in CH_2Cl_2 (200 mL) the product **1** was isolated as a light yellow oil (4.45 g, 96%). R_f 0.31 (20% MeOH in CH_2Cl_2); δ_H (400 MHz; $CDCl_3$) 7.93- 7.82 (4 H, m, ArH), 7.75-7.64 (6 H, m, ArH), 7.51 (1 H, dd, *J* 16.5, 9.5, CH_2=C*H*), 6.72 (1 H, dd, *J* 9.5, 2.5, *H*HC=CH), 6.57 (1 H, dd, *J* 16.5, 2.5, *H*HC=CH); δ_C (100.5 MHz; $CDCl_3$) 138.1 (t), 134.6 (d), 131.6 (d), 130.5 (d), 125.0 (s), 123.4 (d).

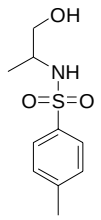
Compound **1** is stable at RT for at least 6 months (we have never observed decomposition during storage), but it is slightly hydroscopic and should be stored appropriately (under nitrogen/argon in a container sealed with parafilm). Sometimes a dark green/black colored product **1** was obtained (this was observed if a bottle of old triflic anhydride was used in the synthesis of 2-bromoethyl trifuoromethanesulfonate) but it could be used in the chemistry described below without detriment.

Synthesis of *N*-sulfonyl β-amino alcohols 2a-2f

General method A[4]

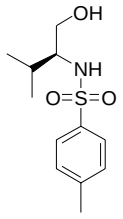
According to the procedure reported by Abiko,[4] the β-amino alcohols **(**4.80-14.97 mmol) were dissolved in dry CH_2Cl_2 (15 mL), cooled to 0 °C and triethylamine (1.2 eq) was added under argon and the reaction stirred for 5 min. The reaction mixture was then treated with tosyl chloride (1.0 eq) and stirred for 1 h. After that the reaction mixture was allowed to warm to RT. After stirring for 2 h the reaction was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 1 M HCl (50 mL), water (50 mL), sat. $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated under vacuum and purified by recrystallization (EtOAc-PE).

(±)-*N*-(2-Hydroxy-1-methylethyl)-4-methylbenzenesulfonamide 2a[5]



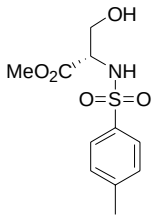
Following general method **A**, using (±)-2-aminopropan-1-ol (0.500 g, 6.66 mmol), triethylamine (0.79 g, 7.8 mmol) and tosyl chloride (1.27 g, 6.66 mmol), after recrystallization, the title compound **2a** was isolated as a colorless crystalline solid (1.42 g, 93%); R_f 0.27 (EtOAc-PE, 4:6); mp 60-61 °C (EtOAc-PE) [lit.[5] mp 63-64 °C (hexane-EtOAc)]; δ_H (400 MHz; $CDCl_3$) 7.77 (2 H, d, *J* 8.5, ArH), 7.35-7.29 (2 H, d, *J* 8.5, ArH), 5.11 (1 H, d, *J* 7.0, NH), 3.58 (1 H, ddd, *J* 10.5, 7.0, 3.5, CH*H*OH), 3.46-3.33 (2 H, m, CH_3C*H*-CH*H*), 2.41 (1H, m, OH), 2.43 (3 H, s, Ar-CH_3), 1.02 (3 H, d, *J* 6.5, CH_3); δ_C (100 MHz, $CDCl_3$) 143.0 (s), 137.6 (s), 129.9 (d), 127.2 (d), 66.3 (t), 51.6 (d), 21.6 (q), 17.7 (q).

***N*-[(1*S*)-1-(Hydroxymethyl)-2-methylpropyl]-4-methylbenzenesulfonamide 2b**[5]



Following general method **A**, using (*S*)-2-amino-3-methylbutan-1-ol (0.50 g, 4.8 mmol), triethylamine (0.58 g, 5.7 mmol) and tosyl chloride (0.92 g, 4.8 mmol), after recrystallization, the title compound **2b** was isolated as a colorless crystalline solid (1.14 g, 92%); R_f 0.2 (EtOAc-PE, 3:7); mp 85-87 °C (EtOAc-PE) [lit.[5] mp 87-89 °C (EtOAc-PE)]; δ_H (400 MHz; $CDCl_3$) 7.77 (2 H, d, *J* 8.5, ArH), 7.29 (2 H, d, *J* 8.5, ArH), 4.95 (1 H, d, *J* 8.5, NH), 3.61-3.52 (2 H, m, CH_2O), 3.06-2.99 (1 H, m, NCH), 2.43 (3 H, s, Ar-CH_3), 2.13 (1 H, br t, *J* 5.5, OH), 1.81-1.71 (1 H, m, $(CH_3)_2CH$), 0.78 (3 H, d, *J* 6.8, CH_3), 0.76 (3 H, d, *J* 6.8, CH_3); δ_c (75 MHz; $CDCl_3$) 143.4 (s), 137.4 (s), 129.6 (d), 127.1 (d), 63.0 (t), 60.9 (d), 29.4 (d), 21.5 (q), 19.0 (q), 18.3 (q).

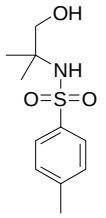
Methyl (2*S*)-3-hydroxy-2-{[(4-methylphenyl)sulfonyl]amino}propanoate 2c[6]



Using a modified version of the procedure reported by Baldwin et al.,[6] L-serine methyl ester hydrochloride (2.33 g, 15.0 mmol) was dissolved in dry CH_2Cl_2 (25 mL), cooled to 0 °C and triethylamine (3.60 g, 35.6 mmol) was added under argon and the reaction stirred for 5 min. The reaction mixture was then treated with tosyl chloride (3.15 g, 16.5 mmol) and stirred for 2 h. After that the reaction mixture was allowed to warm to RT. After stirring for 12 h the reaction was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with sat. $NaHCO_3$ (50 mL), 10% citric acid (50 mL), water (50 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated under vacuum and washed with diethyl ether, the title compound **2c** was isolated as a colorless crystalline solid (3.90 g, 95%); R_f 0.4 (EtOAc-PE, 1:1); mp 83-84 °C (EtOAc-PE) [lit.[6] mp 84-85 °C (EtOAc-hexane]; $[\alpha]_D^{22}$ +10 (*c*. 1.0, CH_2Cl_2) [lit.[6] $[\alpha]_D^{20}$ +12.2 (*c*. 0.83, $CHCl_3$)]; δ_H (400 MHz;

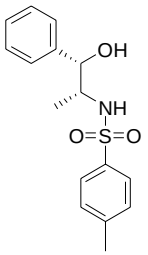
$CDCl_3$) 7.73 (2 H, d, *J* 8.5, ArH), 7.29 (2 H, d, *J* 8.5, ArH), 5.77 (1 H, d, *J* 7.5, NH), 3.98 (1 H, dt, *J* 7.5, 3.5, NCH), 3.89-3.86 (2 H, m, NCHC*H*$_2$), 3.59 (3 H, s, OCH_3), 2.64-2.56 (1 H, m, OH), 2.41 (3 H, s, Ar-CH_3); δ_c (100.5 MHz; $CDCl_3$) 170.2 (s), 144.0 (s), 136.4 (s), 129.8 (d), 127.3 (d), 63.7 (t), 57.6 (d), 53.0 (q), 21.6 (q).

_N_-(2-Hydroxy-1,1-dimethylethyl)-4-methylbenzenesulfonamide 2d[7]



Following general method **A**, using 2-amino-2-methylpropan-1-ol (0.963 g, 10.8 mmol), triethylamine (1.31 g, 12.9 mmol) and tosyl chloride (2.05 g, 10.8 mmol), after recrystallization, the title compound **2d** was isolated as a colorless crystalline solid (2.34 g, 89%); R_f 0.3 (EtOAc-PE, 4:6); mp 94-95 °C (EtOAc-PE) [lit.[7] mp 92-93 °C (hexane)]; δ_H (400 MHz; $CDCl_3$) 7.80 (2 H, d, *J* 8.5, ArH), 7.30 (2 H, d, *J* 8.5, ArH), 5.35 (1 H, br s, NH), 3.45 (2 H, s, C*H*$_2$-OH), 2.85 (1 H, br s, OH), 2.42 (3 H, s, Ar-CH_3), 1.12 (6 H, s, $(CH_3)_2C$); δ_C (100.5 MHz, $CDCl_3$) 143.3 (s), 140.0 (s), 129.7 (d), 127.1 (d), 70.2 (t), 58.0 (s), 24.5 (q), 21.6 (q).

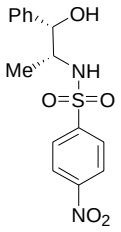
_N_-[(1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-4-methylbenzenesulfonamide 2e[8]



Following general method **A**, using D-(+)-norephedrine (1.00 g, 6.61 mmol), triethylamine (0.79 g, 7.8 mmol) and tosyl chloride (1.25 g, 6.56 mmol), after recrystallization, the title compound **2e** was obtained as colorless crystals (1.65 g, 82%); R_f 0.26 (EtOAc-PE, 2:8); mp 86-87 °C (EtOAc-PE) [lit.[8] mp 86-88 °C (hexane-Et_2O)]; δ_H (400 MHz; $CDCl_3$) 7.78 (2 H, d, *J* 8.5, ArH), 7.32-7.21 (7 H, m, ArH), 4.91 (1 H, d, *J* 9.0, PhCH), 4.78 (1 H, br s, OH), 3.57 (1 H, dqd, *J* 9.0, 7.0, 4.0, NCH), 2.66 (1 H, d, *J* 4.0, NH), 2.42 (3H, s, Ar-CH_3), 0.84 (3 H, d, *J* 7.0, CHC*H*$_3$); δ_c (100 MHz;

$CDCl_3$) 143.6 (s), 140.2 (s), 137.8 (s), 129.8 (d), 128.4 (d), 127.8 (d), 127.1 (d), 126.1 (d), 75.7 (d), 54.9 (d), 21.6 (q), 14.8 (q).

[(1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-4-nitrobenzenesulfonamide 2f



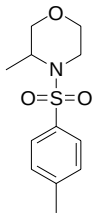
According to the procedure reported by Dioury et al.,[9] D-(+)-norephedrine (0.50 g, 3.3 mmol) was dissolved into THF (10 mL) and cooled to 0 °C. Then sodium hydrogen carbonate (0.80 g, 9.5 mmol) and *p*-nitrophenylsulfonyl chloride (0.80 g, 3.6 mmol) were added and the reaction mixture was allowed to warm to RT and stirred overnight. The crude mixture was concentrated under vacuum and dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (3 × 50 mL), dried over $MgSO_4$ and concentrated. The target compound **2f** was isolated as a white crystalline solid (1.09 g, 98%); R_f 0.36 (EtOAc-PE, 3:7); mp 106-107 °C (EtOAc-PE); $[\alpha]_D^{22}$ +25 (*c*. 0.6, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3509 (OH), 3303 (NH), 1528 (NO_2), 1349 (SO_2), 1162 (SO_2); δ_H (400 MHz; $CDCl_3$) 8.32 (2 H, d, *J* 8.5, ArH), 8.03 (2 H, d, *J* 8.5, ArH), 7.34-7.21 (5 H, m, ArH), 5.06 (1 H, br d, *J* 9.5, NH), 4.78 (1 H, dd, *J* 3.5, 3.5, PhCH), 3.68 (1 H, dqd, *J* 9.5, 6.5, 3.5, NCH), 2.36 (1 H, m, OH), 0.93 (3 H, d, *J* 6.5, CH_3); δ_c (100.5 MHz; $CDCl_3$) 150.0 (s), 146.9 (s), 139.9 (s), 128.6 (d), 128.2 (2 × d), 126.0 (d), 124.4 (d), 76.1 (d), 55.3 (d), 15.4 (q); *m/z* (ESI^+) 359 $[M+Na]^+$; HRMS (ESI^+) $C_{15}H_{16}N_2O_5SNa$ ($M+Na^+$) requires: 359.0676; found: 359.0672. Anal. $C_{15}H_{16}N_2O_5S$ requires: C, 53.56; H, 4.79; N, 8.33; found: C, 53.84; H, 4.75; N, 7.89.

Synthesis of morpholines 3a-3f

General method B

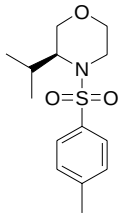
A stirred solution of *N*-tosyl-β-amino alcohol **2a-2e** (0.28-0.68 mmol) or *N*-nosyl-β-amino alcohol **2f** (0.59 mmol) in CH_2Cl_2 (10 mL) was treated with triethylamine (2 eq) at 0 °C under argon. After 10 min a solution of diphenylvinylsulfonium salt **1** (1.05-1.2 eq) in CH_2Cl_2 (5 mL) was added drop-wise over two min and the reaction was stirred for 3 h at 0 °C, followed by 12 h at RT. The reaction was then quenched with saturated ammonium chloride solution (10 mL), extracted with CH_2Cl_2 (3 × 50 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The product was then purified using flash column chromatography on silica.

(±)-3-Methyl-4-[(4-methylphenyl)sulfonyl]morpholine 3a



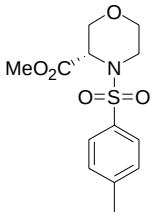
Following general method **B**, (±)-*N*-tosyl-β-amino alcohol **2a** (0.101 g, 0.440 mmol), triethylamine (0.090 g, 0.89 mmol) and diphenylvinylsulfonium salt **1** (0.167 g, 0.461 mmol), after chromatography (EtOAc-PE, 2:8) the title compound **3a** was obtained as a colorless crystalline solid (0.106 g, 94%); R_f 0.4 (EtOAc-PE, 3:7); mp 92-93 °C (EtOAc-PE); ν_{max}(neat)/cm^{-1} 1344 (SO_2), 1154 (SO_2); δ_H (400 MHz; $CDCl_3$) 7.68 (2H, d, *J* 8.5, ArH), 7.29 (1 H, d, *J* 8.5, ArH), 3.90 (1 H, qd, *J* 6.5, 4.5, CH_3CH), 3.83-3.78 (1 H, m, NCH_2CHH), 3.61-3.53 (2 H, m, $NCHCH_2$), 3.50-3.42 (2 H, m, NCH_2CHH, NCH*H*), 3.30-3.21 (1 H, m, NCH*H*), 2.42 (3 H, s, Ar-CH_3), 1.12 (3 H, d, *J* 6.5, CH_3); δ_C (100.5 MHz, $CDCl_3$) 143.5 (s), 137.3 (s), 129.8 (d), 127.2 (d), 71.5 (t), 66.6 (t), 49.2 (d), 40.6 (t), 21.6 (q), 13.9 (q); *m/z* (CI^+) 256 $[M+H]^+$, 100%); HRMS (CI^+) (MH^+) $C_{12}H_{18}NO_3S$ requires: 256.1007; found 256.1005. Anal. $C_{12}H_{17}NO_3S$ requires C, 56.45; H, 6.71; N, 5.49; found: C, 56.13; H, 6.86; N, 5.18.

(3*S*)-3-Isopropyl-4-[(4-methylphenyl)sulfonyl]morpholine 3b



Following general method **B**, *N*-tosyl-β-amino alcohol **2b** (0.072 g, 0.28 mmol), triethylamine (0.060 g, 0.59 mmol) and diphenylvinylsulfonium salt **1** (0.106 g, 0.292 mmol), after chromatography (EtOAc-PE, 2:8) the title compound **3b** was isolated as colorless crystals (0.076 g, 96%); R_f 0.62 (EtOAc-PE, 3:7); mp 99-101 °C (EtOAc-PE); $[\alpha]_D^{20}$ +32 (*c*. 0.5, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1341 (SO_2), 1155 (SO_2); δ_H (400 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.5, ArH), 7.31 (2 H, d, *J* 8.5, ArH), 3.82 (1 H, d, *J* 11.5, CHCH*H*O), 3.66-3.59 (2 H, m, NCH*H*, OCH*H*CH), 3.35-3.10 (4 H, m, NCH*H*CH*H*OCH*H*CH), 2.43 (3 H, s, Ar-CH_3), 2.35-2.20 (1 H, m, Me_2CH), 0.99 (3 H, d, *J* 6.5, CH_3), 0.97 (3 H, d, *J* 6.5, CH_3); δ_c (100.5 MHz; $CDCl_3$) 143.2 (s), 138.8 (s), 129.8 (d), 126.9 (d), 66.1 (t), 65.5 (t), 59.7 (d), 41.2 (t), 25.3 (d), 21.5 (q), 19.9 (q), 19.8 (q); *m/z* (CI^+) 284 $[M+H]^+$; HRMS (CI^+) $C_{14}H_{22}NO_3S$ (MH^+) requires: 284.1320; found: 284.1317. Anal. $C_{14}H_{21}NO_3S$ requires C, 59.34; H, 7.47; N, 4.94; found: C, 59.71; H, 7.58; N, 5.19.

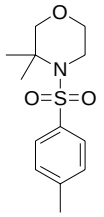
Methyl (3*S*)-4-[(4-methylphenyl)sulfonyl]morpholine-3-carboxylate 3c



Following general method **B**, *N*-tosyl-β-amino alcohol **2c** (1.01 g, 3.70 mmol), triethylamine (0.74 g, 7.3 mmol) and diphenylvinylsulfonium salt **1** (1.40 g, 3.86 mmol), after chromatography (EtOAc-PE, 3:7), the title compound **3c** was isolated as a colorless crystals (1.07 g, 97%); R_f 0.63 (EtOAc-PE, 4:6); mp 98-99 °C (EtOAc-PE); $[\alpha]_D^{22}$ -68 (*c* 1.0, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 1750 (CO), 1347 (SO_2), 1140 (SO_2); δ_H (400 MHz; $CDCl_3$) 7.69 (2 H, d, *J* 8.5, ArH), 7.33 (2 H, d, *J* 8.5, ArH), 4.53 (1 H, d, *J* 3.0, NCH), 4.30 (1 H, d, *J* 11.5, NCHCH*H*), 3.89 (1 H, dd, *J* 11.5, 3.0, NCH_2CH*H*), 3.73 (1 H, dd, *J* 11.5, 3.0, NCHCH*H*), 3.62-3.45 (6 H, m, O*C*H_3, N*C*H_2CH*H*), 2.45 (3 H, s, Ar-

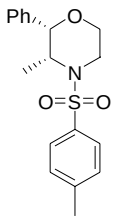
CH_3); δ_c (100.5 MHz; $CDCl_3$) 169.5 (s), 143.7 (s), 136.4 (s), 129.6 (d), 127.4 (d), 68.8 (t), 66.7 (t), 55.4 (d), 52.4 (q), 42.0 (t), 21.6 (q); *m/z* (CI^+) 300 $[M+H]^+$; HRMS (CI^+) (MH^+) $C_{13}H_{18}NO_5S$ requires: 300.0906; found: 300.0904. Anal. $C_{13}H_{17}NO_5S$ requires: C, 52.16; H, 5.72; N, 4.68; S 10.71; found: C, 52.60; H, 5.63; N, 4.91; S, 10.75.

3,3-Dimethyl-4-[(4-methylphenyl)sulfonyl]morpholine 3d



Following general method **B**, *N*-tosyl-β-amino alcohol **2d** (0.151 g, 0.621 mmol), triethylamine (0.125 g, 1.24 mmol) and diphenylvinylsulfonium salt **1** (0.235 g, 0.648 mmol), after chromatography (EtOAc-PE, 2:8) the title compound **3d** was obtained as colorless needles (0.161 g, 96%); R_f 0.45 (30:70 EtOAc-PE); mp 105-106 °C (EtOAc-PE); ν_{max}(neat)/cm^{-1} 1343 (SO_2), 1154 (SO_2); δ_H (400 MHz; $CDCl_3$) 7.70 (2 H, d, *J* 8.5, ArH), 7.30 (2 H, d, *J* 8.5, ArH), 3.78-3.74 (2 H, m, OCH_2CH_2), 3.50-3.47 (2 H, m, NCH_2), 3.28 (2 H, s, $NCCH_2$), 2.43 (3 H, s, Ar-CH_3) 1.26 (6 H, s, 2 × CH_3); δ_C (100.5 MHz, $CDCl_3$) 143.2 (s), 139.2 (s), 129.6 (d), 127.2 (d), 78.1 (t), 67.7 (t), 57.4 (s), 43.1 (t), 22.4 (q), 21.5 (q); *m/z* (CI^+) 270 $[M+H]^+$; HRMS (CI^+) (MH^+) $C_{13}H_{20}NO_3S$ requires: 270.1164; found: 270.1156. Anal. $C_{13}H_{19}NO_3S$ requires: C, 57.97; H, 7.11; N, 5.20; found: C, 57.77; H, 7.17; N, 5.41.

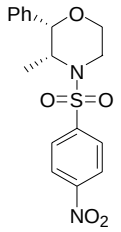
(2*S*,3*R*)-3-Methyl-4-[(4-methylphenyl)sulfonyl]-2-phenylmorpholine 3e



Following general method **B**, *N*-tosyl-β-amino alcohol **2e** (0.210 g, 0.688 mmol), triethylamine (0.14 g, 1.4 mmol) and diphenylvinylsulfonium salt **1** (0.260 g, 0.717 mmol) after chromatography (EtOAc-PE, 2:8) the title compound **3e** was isolated as a white gummy solid (0.224 g, 98%); R_f 0.67 (EtOAc-PE, 2: 8); $[\alpha]_D^{20}$ +12 (*c*. 1.0,

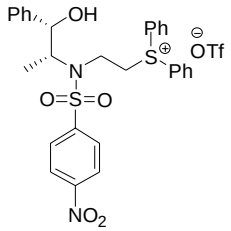
$CHCl_3$); ν_{max}(neat)/cm^{-1} 1340 (SO_2), 1157 (SO_2); δ_H (400 MHz; $CDCl_3$) 7.74 (2 H, d, *J* 8.5, ArH), 7.35-7.22 (7 H, m, ArH), 4.63 (1 H, d, *J* 3.0, PhCH), 4.20 (1 H, dq, *J* 7.0, 3.0, NC*H*Me), 4.05 (1 H, dd, *J* 12.5, 3.0, OCH_{eq}H), 3.70 (1 H, ddd, *J* 12.5, 12.5, 3.0, OCHH_{ax}), 3.60 (1 H, dd, *J* 12.5, 3.0, NCH_{eq}H), 3.25 (1 H, ddd, *J* 12.5, 12.5, 3.0, NCHH_{ax}), 2.43 (3 H, s, Ar-CH_3), 0.72 (3 H, d, *J* 7.0, CH-CH_3); δ_c (100.5 MHz; $CDCl_3$) 143.4 (s), 138.7 (s), 137.9 (s), 129.8 (d), 128.3 (d), 127.4 (d), 127.2 (d), 125.4 (d), 80.4 (d), 67.1 (t), 53.3 (d), 39.5 (t), 21.4 (q), 9.2 (q); *m/z* (ESI^+) 332 $(M+H)^+$; HRMS (ESI^+) $C_{18}H_{22}NO_3S$ (MH^+) requires: 332.1326; found: 332.1314. Anal. $C_{18}H_{21}NO_3S$ requires: C, 65.23; H, 6.39; N, 4.23; found: C, 65.09; H, 6.73; N, 4.17.

(2*S*,3*R*)-3-Methyl-4-[(4-nitrophenyl)sulfonyl]-2-phenylmorpholine 3f



Following general method **B**, *N*-nosyl-β-amino alcohol **2f** (0.199 g, 0.592 mmol), triethylamine (0.120 g, 1.19 mmol) and diphenylvinylsulfonium salt **1** (0.226 g, 0.624 mmol), after column chromatography (EtOAc-PE, 3:7) the title compound **3f** was isolated as pale yellow crystals (0.211 g, 98%); R_f 0.58 (EtOAc-PE, 3:7); mp 133-134 °C (EtOAc-PE); $[\alpha]_D^{22}$ +25 (*c*. 0.2, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 1527 (NO_2), 1348 (SO_2), 1157 (SO_2); δ_H (400 MHz; $CDCl_3$) 8.40 (2 H, d, *J* 8.5, ArH), 8.06 (2 H, d, *J* 8.5, ArH), 7.37-7.23 (5 H, m, ArH), 4.69 (1 H, d, *J* 2.5, PhCH), 4.26 (1 H, dq, *J* 6.5, 2.5, NC*H*Me), 4.14 (1 H, dd, *J* 12.5, 3.5, OCH_{eq}H), 3.77 (1 H, ddd, *J* 12.5, 12.5, 3.5, OCH_{ax}H), 3.66 (1 H, dd, *J* 12.5, 3.5, NCH_{eq}H), 3.31 (1 H, ddd, *J* 12.5, 12.5, 3.5, NCH_{ax}H), 0.75 (3 H, d, *J* 6.5, CH_3); δ_c (100.5 MHz; $CDCl_3$) 150.1 (s), 146.6 (s), 138.2 (s), 128.5 (d), 128.3 (d), 127.8 (d), 125.4 (d), 124.6 (d), 80.6 (d), 67.2 (t), 53.7 (d), 39.7 (t), 9.4 (q); *m/z* (CI^+) 363 $[M+H]^+$; HRMS (CI^+) $C_{17}H_{19}N_2O_5S$ (MH^+) requires: 363.1015; found: 363.1023.

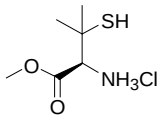
Isolation of protonated 5f: *N*-[(1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-(2-{[4-nitrophenyl)sulfonyl]amino} ethyl) (diphenyl) sulfonium trifluoromethane sulfonate



Following general method **B**, using *N*-nosyl-β-amino alcohol **2f** (0.199 g, 0.592 mmol), triethylamine (0.120 g, 1.19 mmol) and diphenylvinylsulfonium salt **1** (0.260 g, 0.717 mmol), after 3 h stirring at 0 °C (monitored by TLC) followed by chromatography (EtOAc-PE, 8:2) the title compound (protonated-**5f**) was isolated as pale yellow crystals (0.272 g, 66%); R_f 0.3 (EtOAc); [NMR data were obtained immediately because with the passage of time protonated-**5f** cyclized to morpholine **3f**] δ_H (400 MHz; $CDCl_3$) 8.30 (2 H, d, *J* 8.5, ArH), 8.08-8.03 (4 H, m, ArH), 7.88 (2 H, d, *J* 8.5, ArH), 7.77-7.67 (6 H, m, ArH), 7.31-7.2 (5 H, m, ArH), 5.05 (1H, br dd, *J* 5.5, 2.5, PhCH), 4.93 (1 H, dt, *J* 12.5, 5.5, SCH*H*), 4.66 (1 H, dt, *J* 12.5, 7.5, SCH*H*), 4.24 (1 H, d, *J* 5.5, OH), 3.94 (1 H, qd, *J* 7.5, 2.5, NCH), 3.86-3.75 (2 H, m, NCH_2), 0.70 (3 H, d, *J* 7.5, CH_3); δ_c (100.5 MHz; $CDCl_3$) 150.3 (s), 144.3 (s), 141.5 (s), 134.8 (d), 134.6 (d), 131.6 (d), 131.0 (d), 130.6 (d), 128.5 (d), 128.4 (d), 127.6 (d), 125.5 (d), 124.9 (s), 124.7 (d), 123.9 (s), 77.0 (d), 60.0 (d), 46.0 (t), 39.8 (t), 8.8 (q).

Synthesis of thiomorpholines 3g-3i

Methyl (*S*)-2-amino-3-mercapto-3-methylbutanoate 2i[10,11]



According to the procedure reported by Chvapil et al.,[10] D-penicillamine (2.50 g, 16.8 mmol) was dissolved in methanol (50 mL), cooled to 0 °C, and thionyl chloride (12.5 mL, 171 mmol) was added from a burette, the reaction mixture was allowed to warm to RT and stirred for 3 d. On the second day additional thionyl chloride (2.5 mL) was added. After 3 d, the reaction mixture was refluxed for 2-3 h, during which time most of the excess thionyl chloride was removed. The reaction mixture was reduced to about 20 mL under vacuum, and after addition of ether the product precipitated and was isolated by filtration. Recrystallization with MeOH and diethyl ether yielded the desired product **2i** as colorless crystals (2.40 g, 72%); mp 140-142 °C (MeOH-Et_2O); δ_H (400 MHz; CD_3OD) 4.12 (1 H, s, NCH), 3.86 (3 H, s, OCH_3), 1.56 (3 H, s, CH_3), 1.47 (3 H, s, CH_3); δ_c (100.5 MHz; CD_3OD) 167.5 (s), 62.7 (d), 52.3 (q), 43.5 (s), 29.7 (q), 27.2 (q).

General method C

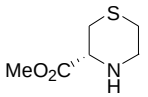
To a stirred solution of β-amino thiols **2g-2i** (0.116-1.29 mmol) in CH_2Cl_2 (5-10 mL) at 0 °C was added dry triethylamine (2-3 eq). After 10 min a solution of diphenylvinylsulfonium salt **1** (1.05-1.1 eq) in CH_2Cl_2 (5 mL) was added drop wise over two min. The reaction mixture was stirred for 3 h at 0 °C and then 12 h at RT. The reaction was quenched with saturated ammonium chloride solution (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The aqueous layer was basified with 5% Na_2CO_3 solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and dried over anhydrous K_2CO_3, filtered and evaporated under vacuum.

Thiomorpholine 3g

Following general method **C**, using cysteamine (0.100 g, 1.30 mmol), triethylamine (0.260 g, 2.57 mmol) and diphenylvinylsulfonium salt **1** (0.492 g, 1.36 mmol), after

chromatography (Et_2O-Et_3N, 95:5), the title compound **3g** was isolated as a colorless oil (0.131 g, 98%); R_f 0.27 (Et_2O-Et_3N, 95:5); δ_H (400 MHz; $CDCl_3$) 3.14-3.09 (4 H, m, NCH_2), 2.62-2.57 (4 H, m, SCH_2), 1.56 (1 H, br s, NH); δ_c (100 MHz; $CDCl_3$) 49.8 (t), 28.4 (t) [data are the same as for commercially available material].

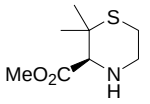
Thiomorpholine-(3*R*)-carboxylic acid methyl ester 3h and thiomorpholine-(3*R*)-carboxylic acid methyl ester hydrochloride 8



Following general method **C**, using L-cysteine methyl ester hydrochloride (0.0206 g, 0.120 mmol), triethylamine (0.0340 g, 0.336 mmol) and diphenylvinylsulfonium salt **1** (0.0500 g, 0.138 mmol), after chromatography (Et_2O-Et_3N, 95:5) the title compound **3h** was isolated as a colorless gummy solid (0.0185 g, 96%); R_f 0.7 (Et_2O-Et_3N, 95:5); $[\alpha]_D^{20}$ -38 (*c*. 0.6, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3398 (NH), 1744 (CO); δ_H (400 MHz; $CDCl_3$) 3.79 (4 H, m, NC*H*, OCH_3), 3.46 (1 H, ddd, *J* 12.5, 5.0, 3.0, NCH_{eq}H), 3.10 (1 H, ddd, *J* 12.5, 10.0, 3.0, NCHH_{ax}), 2.95-2.83 (2 H, m, SCH_2CH), 2.74 (1 H, ddd, *J* 13.5, 10.0, 3.0, $NCH_2CH$$H_{ax}$), 2.57-2.51 (1 H, m, NCH_2CH_{eq}H), 1.26 (1 H, br s, NH); δ_c (100 MHz; $CDCl_3$) 171.5 (s), 58.3 (d), 52.5 (q), 46.6 (t), 29.2 (t), 27.2 (t); *m/z* (ESI^+) 162 $(M+H)^+$; HRMS (ESI^+) $C_6H_{12}NO_2S$ (MH^+) requires: 162.0588; found: 162.0583.

3h (0.010 g, 0.062 mmol) was dissolved into dry diethyl ether (1 mL) and treated with 2 M HCl in diethylether (1 mL). The hydrochloride **8**[12] was isolated by filtration as a colorless solid (0.011 g, 90%); mp 172-173 °C (MeOH-Et_2O) [lit.[12] mp 172-173 °C (MeOH-Et_2O)]; $[\alpha]_D^{23}$ -21 (*c*. 1.0, CH_3OH) [lit.[12] $[\alpha]_D^{25}$ -20.4 (*c*. 1, CH_3OH)]; δ_H (400 MHz; D_2O) 4.36 (1 H, dd, *J* 9.5, 3.5, NC*H*), 3.83 (3 H, s, OCH_3), 3.71 (1 H, ddd, *J* 13.0, 5.0, 3.5, NCH*H*), 3.36 (1 H, ddd, 13.0, 8.5, 3.5, NCH*H*), 3.22-2.72 (4 H, m, CH_2SCH_2); δ_c (100 MHz; $CDCl_3$) 168.2 (s), 56.6 (d), 53.9 (q), 45.0 (t), 26.2 (t), 23.5 (t).

Methyl (3*S*)-2,2-dimethylthiomorpholine-3-carboxylate 3i



Following general method **C**, using methyl (*S*)-2-amino-3-mercapto-3-methylbutanoate hydrochloride (0.150 g, 0.751 mmol), triethylamine (0.225 g, 2.22 mmol) and diphenylvinylsulfonium salt **1** (0.310 g, 0.855 mmol), after chromatography (Et_2O-Et_3N, 95:5), the title compound **3i** was isolated as a colorless gummy solid (0.134 g, 94%); R_f 0.68 (Et_2O-Et_3N, 95:5); $[\alpha]_D^{21}$ +40 (*c*. 0.5, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3340 (NH), 2952 (CH), 2928 (CH), 1734 (CO); δ_H (400 MHz; $CDCl_3$) 3.70 (4 H, s, OCH_3, NCH), 3.36-3.46 (1 H, m, NCH*H*), 2.87-2.97 (2 H, m, NCH*H*CH*H*), 2.24-2.34 (1 H, m, NCH_2CH*H*), 2.14 (1 H, br s, NH), 1.41 (3 H, s, CH_3), 1.28 (3 H, s, CH_3); δ_c (100.5 MHz; $CDCl_3$) 171.0 (s), 69.0 (d), 51.8 (q), 46.7 (t), 39.2 (s), 28.0 (q), 26.3 (t), 22.3 (q); *m/z* (CI^+) 190 $[M+H]^+$; HRMS (CI^+) (MH^+) $C_8H_{16}NO_2S$ requires: 190.0902, found: 190.0905.

Synthesis of piperazines 3j-3m

General method D

The diamines **2j**, **2k**, or *N*-tosyl diamines **2l**,[13] **2m** (0.234-0.47 mmol) were dissolved into anhydrous CH_2Cl_2 (10 mL), stirred at 0 °C under argon and treated with either triethylamine (2 eq) or DBU (2 eq; when *N*-tosyl diamines were used). After 10 min a solution of diphenylvinylsulfonium salt **1** (1.05 eq) in CH_2Cl_2 (5 mL) was added drop wise over two min. The reaction mixture was further stirred for 2 h at 0 °C and then allowed to warm to RT overnight.

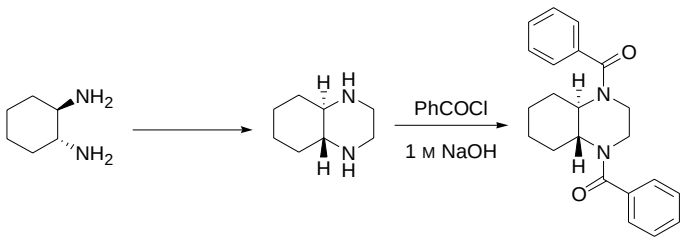
a) Workup for *N*-H-piperazines

The reaction was quenched with water and the solution was acidified with dil. HCl and extracted with CH_2Cl_2 (3 × 20 mL). The aqueous layer was basified with sat. K_2CO_3 solution and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous K_2CO_3, filtered and evaporated under vacuum. The products were then purified using flash column chromatography on silica.

b) Workup for *N*-tosyl piperazines

When making *N*-tosyl piperazines the reaction mixture was quenched with sat. ammonium chloride solution and extracted with CH_2Cl_2 (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum. The products were then purified using flash column chromatography on silica.

(±)-1,4-Dibenzoyldecahydroquinoxaline 3j

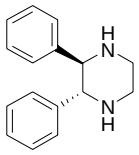


3j

Following general method **D**, using (±)-*trans*-1,2-diaminocyclohexane **2j** (0.173 g, 1.52 mmol), triethylamine (0.308 g, 3.04 mmol) and diphenylvinylsulfonium salt **1** (0.575 g, 1.59 mmol), after overnight stirring, the solvent was removed under vacuum. The residue was dissolved in 1 M NaOH (4.56 mL), stirred, cooled to 0 °C and treated with benzoyl chloride (0.640 g, 4.55 mmol). The reaction mixture was allowed to warm to RT and stirred for 3 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic phases were washed with dil. HCl, brine, dried over $MgSO_4$,

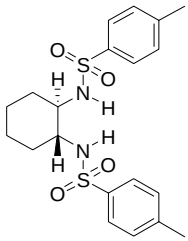
filtered and evaporated. The target amide **3j** was obtained as a white solid (0.519 g, 98%); R_f 0.44 (EtOAc-PE, 4:6); mp 60-61 °C (EtOAc-PE); ν_{max}(neat)/cm^{-1} 1630 (NCO); δ_H (400 MHz; $CDCl_3$) 7.45-7.34 (10 H, m, ArH), 3.89-3.80 (2 H, m, NCH), 3.71-3.61 (2 H, m, NC*H*H), 3.56-3.49 (2 H, m, NCH*H*), 2.41-2.30 (2 H, m), 1.79-1.71 (2 H, m), 1.67-1.53 (2 H, m), 1.46-1.30 (2 H, m); δ_c (100.5 MHz; $CDCl_3$) 173.2 (s), 136.4 (s), 130.4 (d), 128.5 (d), 127.6 (d), 58.6 (d), 46.0 (t), 30.2 (t), 25.4 (t); *m/z* (EI$^+$) 349 (M+H)$^+$; HRMS (EI$^+$) (M$^+$) $C_{22}H_{24}N_2O_2$ requires: 348.1838; found: 348.1838.

(2*R*,3*R*)-Diphenylpiperazine 3k[14]



Following general method **D**, using diamine **2k** (0.050 g, 0.24 mmol), triethylamine (0.047 g, 0.46 mmol) and diphenylvinylsulfonium salt **1** (0.089 g, 0.25 mmol), after chromatography (Et_2O-Et_3N, 9:1); the title compound **3k** was isolated as a white solid (0.052 g, 91%); mp 96-98 °C (Et_2O-PE) [lit.[14] mp 94-96 °C]; δ_H (400 MHz; $CDCl_3$) 7.13-7.06 (10 H, m, ArH), 3.70 (2 H, s, NCH), 3.15-3.05 (4 H, m, NCH_2), 2.51 (2 H, br s, NH); δ_c (100 MHz; $CDCl_3$) 140.6 (s), 128.2 (d), 128.0 (d), 127.5 (d), 67.9 (d), 46.8 (t).

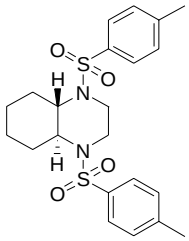
(±)-*N*,*N*-Bistosyl-1,2-*trans*-cyclohexanediamine 2l[13]



A stirred solution of (±)-*trans*-1,2-diaminocyclohexane **2j** (0.390 g, 3.42 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with triethylamine (0.692 g, 6.84 mmol) under argon. Tosyl chloride (1.4 g, 7.3 mmol) was added and stirred for 1 h. The reaction mixture was allowed to warm to RT and stirred overnight. The reaction was quenched with water (50 mL), extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with 1 M HCl (50 mL), water (50 mL), sat. $NaHCO_3$ (50 mL), brine (50 mL) and dried over $MgSO_4$, filtered and concentrated under vacuum and

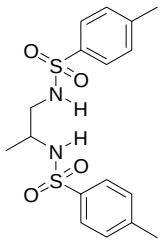
after chromatography (EtOAc-PE, 3:7) the title compound **2l** was isolated as a colorless crystalline solid (1.03 g, 71%); R_f 0.37 (EtOAc-Pet Ether, 4: 6); mp 186-188 °C (EtOAc-PE) [lit.[13] 180-181 °C]; δ_H (400 MHz; $CDCl_3$) 7.76 (4 H, d, *J* 8.5, ArH), 7.32 (4 H, d, *J* 8.5, ArH), 4.85 (2 H, d, *J* 5.5, NH), 2.74 (2 H, m, NCH), 2.43 (6 H, s, Ar-CH_3), 1.85 (2 H, d, *J* 11.5), 1.56 (2 H, d, *J* 6.5), 1.11 (4 H, m); δ_c (100.5 MHz; $CDCl_3$) 143.7 (s), 137.0 (s), 129.8 (d), 127.3 (d), 56.7 (d), 33.5 (t), 24.3 (t), 21.6 (q).

(±)-1,4-Bis(toluene-4-sulfonyl)decahydroquinoxaline 3l



Following general method **D**, using bis-*N*-tosyl diamine **2l** (0.020 g, 0.047 mmol), DBU (0.015 g, 0.099 mmol) and diphenylvinylsulfonium salt **1** (0.019 g, 0.052 mmol), after chromatography (EtOAc-PE, 4:6) the title compound **3l** was isolated as a colorless crystalline solid (0.021 g, 99%); R_f 0.55 (EtOAc-PE, 4:6); mp 127-129 °C (EtOAc-PE); ν_{max}(neat)/cm^{-1} 1342 (SO_2), 1158 (SO_2); δ_H (400 MHz; $CDCl_3$) 7.63 (4 H, d, *J* 8.0, ArH), 7.32 (4 H, d, *J* 8.0, ArH), 3.96-3.82 (2 H, m NCH*H*), 3.24-3.10 (2 H, m, NC*H*H), 2.92-2.81 (2 H, m, NC*H*), 2.36-2.26 (2 H, m), 1.70-1.58 (2 H, m), 1.54-1.38 (2 H, m), 1.20-1.12 (2 H, m); δ_c (100.5 MHz; $CDCl_3$) 143.8 (s), 137.9 (s), 129.9 (d), 127.2 (d), 62.1(d), 46.89 (t), 30.9 (t), 24.7 (t), 21.6 (q); *m/z* (ESI^+) 449 $[M+H]^+$; HRMS (ESI^+) $C_{22}H_{29}N_2O_4S_2$ (MH^+) requires: 449.1561; found: 449.1563;

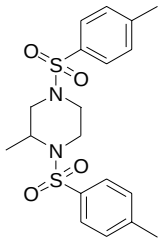
(±)-*N*,*N*-(Propane-1,2-diyl)bis(4-methylbenzenesulfonamide) 2m[16]



A stirred solution of (±)-propan-1,2-diamine (0.50 g, 6.7 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with triethylamine (1.48 g, 14.6 mmol) under argon. Tosyl chloride (2.57 g, 13.5 mmol) was added and the reaction mixture was stirred for

1 h. Then the reaction mixture was allowed to warm to RT and stirred overnight. The reaction was quenched with water (50 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was washed with 1 M HCl (50 mL), water (50 mL), sat. $NaHCO_3$ (50 mL), brine (50 mL) and dried over $MgSO_4$, filtered and concentrated under vacuum. After chromatography (EtOAc-PE, 2:8) the title compound **2m** was isolated as a white solid (2.10 g, 82%); R_f 0.1 (EtOAc-PE, 3:7); mp 107-109 °C (EtOAc-PE); δ_H (400 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.5, ArH), 7.68 (2 H, d, *J* 8.5, ArH), 7.30-7.24 (4 H, m, ArH), 5.32 (1 H, br s, NH), 5.18 (1 H, br s, NH), 3.34-3.30 (1 H, m, NC*H*CH_2), 2.94 (1 H, ddd, *J* 13.5, 6.5, 4.5, NCH*H*), 2.87-2.80 (1 H, m, NCH*H*), 2.40 (3 H, s, Ar-CH_3), 2.39 (3 H, s, Ar-CH_3), 0.96 (3 H, d, *J* 6.5, CH_3); δ_c (100.5 MHz; $CDCl_3$) 143.7 (s), 143.5 (s), 137.2 (s), 136.7 (s), 129.9 (2 × d), 129.8 (d), 127.2 (d), 127.1 (d), 49.5 (d), 48.3 (t), 21.7 (q), 21.6 (q), 18.7 (q).

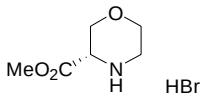
(±)-2-Methyl-1,4-ditosylpiperazine 3m



Following general method **D**, using bis-*N*-tosyl diamine **2m** (0.115 g, 0.301 mmol), DBU (0.092 g, 0.60 mmol) and diphenylvinylsulfonium salt **1** (0.114 g, 0.315 mmol), after chromatography (EtOAc-PE, 4:6) the title compound **3m** was isolated as a white solid (0.120 g, 98%); R_f 0.33 (EtOAc-PE, 3:7); mp 175-177 °C (EtOAc-PE); ν_{max}(neat)/cm^{-1} 1341 (SO_2), 1161 (SO_2); δ_H (400 MHz; $CDCl_3$) 7.62 (2 H, d, *J* 8.5, ArH), 7.57 (2 H, d, *J* 8.5, ArH), 7.33 (2 H, d, *J* 8.0, ArH), 7.26 (2 H, d, *J* 8.0, ArH), 4.21-4.12 (1 H, m, NCH), 3.72-3.60 (2 H, m, NCHCH_2), 3.44 (1 H, ddd, *J* 12.5, 3.5, 3.5, NCHH_{eq}), 3.20 (1 H, ddd, 12.5, 12.5, 3.5, NCHH_{ax}), 2.45 (4 H, m, NCH*H*, Ar-CH_3), 2.41 (3 H, s, Ar-CH_3), 2.32 (1 H, ddd, *J* 12.5, 12.5, 3.5, NCHH_{ax}), 1.09 (3 H, d, *J* 6.5, CHCH_3); δ_c (100.5 MHz; $CDCl_3$) 144.1 (s), 143.7 (s), 137.1 (s), 132.3 (s), 129.9 (2 × d), 127.6 (d), 127.0 (d), 51.1 (t), 48.5 (d), 45.9 (t), 39.6 (t), 21.7 (q), 21.6 (q), 14.0 (q); *m/z* (CI^+) 409 $(M+H)^+$; HRMS (CI^+) $C_{19}H_{25}N_2O_4S_2$ (MH^+) requires: 409.1256; found: 409.1252. Anal. $C_{19}H_{24}N_2O_4S_2$ requires: C, 55.86; H, 5.92; N, 6.86; S, 15.70; found: C, 56.30; H, 5.94; N, 7.18; S, 15.64.

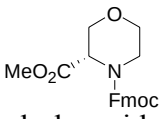
Synthesis of (3*S*) 4-[(9*H*-Fluoren-9-ylmethoxy)carbonyl] morpholine-3-carboxylic acid 6

Methyl (3*S*)-morpholine-3-carboxylate hydrobromide 9



According to the procedure reported by Sannamu et al.,[17] a solution of *N*-tosyl morpholine **3c** (0.100 g, 0.334 mmol), phenol (0.062 g, 0.66 mmol) and 45% HBr in acetic acid (0.7 mL) was stirred at RT for 16 h. After this the reaction mixture was poured into anhydrous ether (5 mL) and a precipitate formed. The precipitate was removed by filtration, washed with ether (15 mL) and dried under high vacuum. The target compound **9** was isolated as a light yellow solid (0.070 g, 94%); mp 138-140 °C (decomposed) (MeOH-Et_2O); $[\alpha]_D^{22}$ -7.5 (*c*. 0.4, CH_3OH); ν_{max}(neat)/cm^{-1} 3383 (NH), 1743 (CO); δ_H (400 MHz; $CDCl_3$) 4.36 (1 H, dd, *J* 8.5, 4.0, NC*H*), 4.22 (dd, 1 H, *J* 12.5, 4.0, NCHCH*H*), 3.98 (1 H, ddd, *J* 12.5, 4.0, 4.0, NCH_2CH*H_{eq}), 3.90 (1 H, dd, *J* 12.5, 8.5, NCHCH*H*), 3.87 (3 H, s, OCH_3), 3.78 (1 H, ddd, *J* 12.5, 9.5, 3.5, NCH_2CH*H_{ax}), 3.43 (1 H, ddd, *J* 12.5, 4.5, 3.5, $NCH*H_{eq}$), 3.27 (1 H, ddd, 12.5, 9.5, 3.5, $NCH*H_{ax}$); δ_c (100.5 MHz; $CDCl_3$) 168.0 (s), 66.6 (t), 64.9 (t), 56.3 (d), 54.3 (q), 43.8 (t); *m/z* (CI^+) 146 (MH^+-HBr); HRMS (CI^+) (M^+-Br) $C_6H_{12}NO_3$ requires: 146.0817; found: 146.0812.

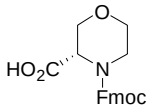
4-(9*H*-Fluoren-9-ylmethyl) 3-methyl (*S*)-morpholine-3,4-dicarboxylate 10[15]



To a stirred solution of morpholine hydrobromide **9** (0.050 g, 0.22 mmol) in 2:1 water-dioxane (2 mL) was added $NaHCO_3$ (0.055 g, 0.65 mmol), and the mixture was cooled to 0 °C. A solution of Fmoc-Cl (0.062 g, 0.24 mmol) in dioxane (2 mL) was then added dropwise, the reaction mixture was allowed to warm to RT and after 3 h stirring, ethyl acetate (20 mL) was added. The organic phase was separated and it was washed with 1 M HCl, brine and dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by preparative TLC (EtOAc-PE, 3:7) to afford the target compound

10 as a white foam (0.080 g, 99%); R_f 0.45 (EtOAc-PE, 3:7); $[\alpha]_D^{22}$ -51.2 (*c*. 1.0, CH_2Cl_2) [lit.[15] $[\alpha]_D^{24}$ -51.5 (*c*. 1, CH_2Cl_2)]; δ_H (400 MHz; $CDCl_3$) mixture of rotamers 7.76 (2 H, t, *J* 7.0), 7.59 (1 H, t, *J* 8.5), 7.50 (1 H, t, *J* 7.0), 7.43-7.37 (2 H, m) 7.35-7.27 (2 H, m), 4.65 (0.5 H, br d, *J* 3.5), 4.56-4.20 (4.5 H, m), 3.94-3.80 (1.5 H, m), 3.78 and 3.73 (3 H, s), 3.66 (1 H, ddd, *J* 12.0, 12.0, 3.5), 3.58 (0.5 H, dd, *J* 12.0, 3.5), 3.50-3.40 (1.5 H, m), 3.22 (0.5 H, td, *J* 12.5, 3.5); δ_c (100.5 MHz; $CDCl_3$) 169.8 (s), 156.0 (s), 155.4 (s), 143.7 (s), 143.5 (s), 143.4 (s), 143.3 (s), 141.1 (s), 140.0 (s), 127.5 (d), 127.4 (d), 127.3 (d), 127.2 (d), 126.8 (d), 126.7 (d), 124.8 (d), 124.7 (d), 124.4 (d), 124.3 (d), 119.8 (d), 119.7 (d), 67.7 (t), 67.4 (t), 67.3 (t), 67.0 (t), 66.3 (t), 66.0 (t), 54.6 (d), 54.1 (d), 52.3 (q), 46.9 (d), 41.3 (t), 40.8 (t).

(3*S*) 4-[(9*H*-Fluoren-9-ylmethoxy)carbonyl] morpholine-3-carboxylic acid 6

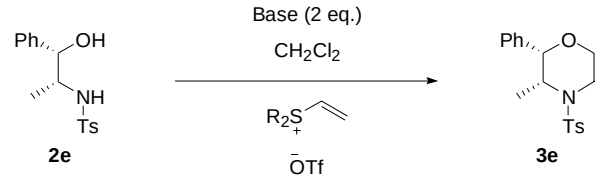


According to the procedure reported by the Guarna and co-workers,[15] the ester **10** (0.0260 g, 0.0708 mmol) was dissolved in dioxane (2 mL) and treated with 5 M HCl (0.5 mL). After 16 h reflux, the reaction mixture was diluted with 5% Na_2CO_3 (5 mL), washed with diethyl ether (3 × 5 mL) and conc. HCl was added to the aqueous layer until the pH was 1. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford the title compound **6** as a white solid (0.0245 g, 98%); mp 128-129 °C [lit.[15] mp 128-130 °C]; $[\alpha]_D^{22}$ -56.5 (*c*. 1, CH_2Cl_2) [lit.[15] $[\alpha]_D^{24}$ -56.9 (*c*. 1, CH_2Cl_2)]; δ_H (400 MHz; $CDCl_3$), mixture of rotamers, 7.69 (1 H, d, *J* 7.5, ArH), 7.65 (1 H, t, *J* 7.5, ArH), 7.51 (1 H, dd, *J* 7.5, 4.5, ArH), 7.43 (1 H, dd, *J* 11.5, 7.5, ArH), 7.34-7.18 (4 H, m, ArH), 4.63 (0.5 H, d, *J* 3.5), 4.52-4.43 (1.5 H, m), 4.41-4.32 (1 H, m), 4.27-4.12 (2 H, m), 3.86-3.81 (1 H, m), 3.75-3.55 (1.5 H, m), 3.49 (0.5 H, dd, *J* 11.5, 3.5), 3.44-3.32 (1.5 H, m), 3.20 (0.5 H, ddd, *J* 12.5, 12.5, 3.4 Hz); δ_c (100.5 MHz; $CDCl_3$) 175.0 (s), 174.8 (s), 156.3 (s), 155.6 (s), 143.7 (s), 143.6 (s), 141.2 (s, 2 C), 127.6 (d, 2 × C), 127.0 (d, 2 × C), 124.9 (d), 124.7 (d), 124.5 (d), 119.9 (d, 2 × C), 67.9 (t), 67.4_1 (t), 67.4_0 (t), 67.0 (t), 66.5 (t), 66.2 (t), 54.5 (d), 54.1 (d), 47.0 (d), 41.4 (t), 40.9 (t).

Use of different vinyl sulfonium salts in the annulation reaction

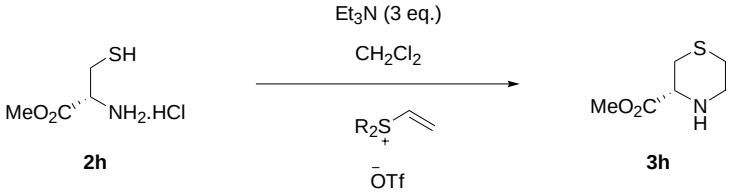
The effectiveness of different vinyl sulfonium salts was assessed using two test substrates **2e** and **2h** (Table 1 and 2). Diphenyl vinyl sulfonium salt **1** was found to be the most effective.

Table 1: The synthesis of morpholine **3e** using diisopropylvinyl and tetrahydrothiophenevinyl sulfonium salts.



Entry	R_2S	Base	Temp (°C)	Time (h)	Yield (%)
1	*i*-Pr_2S	Et_3N	0	3	0
2	*i*-Pr_2S	NaH	0	3	37
3	-$(CH_2)_4$-S	Et_3N	0	3	35
4	-$(CH_2)_4$-S	NaH	0-RT	18	34
5	Ph_2S	Et_3N	0-RT	15	98

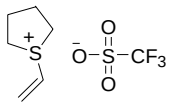
Table 2: The synthesis of thiomorpholine **3h** with diisopropylvinyl and tetrahydrothiophenevinyl sulfonium salt.



Entry	R_2S	Temp (°C)	Time (h)	Yield (%)
1	Ph_2S	0-RT	15	96
2	*i*-Pr_2S	0	15	98
3	-$(CH_2)_4$-S	0-RT	18	20

Diisopropyl(vinyl)sulfonium trifluoromethanesulfonate was synthesized according to a literature procedure.[2]

1-vinyltetrahydro-1*H*-thiophenium trifluoromethanesulfonate 11

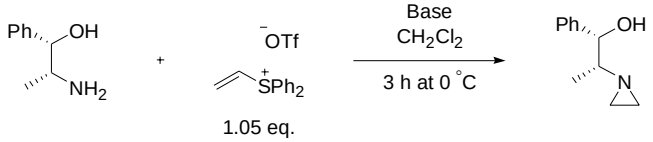


A solution of 2-bromoethyl trifluoromethanesulfonate[2] (3.40 g, 13.2 mmol) in CH_2Cl_2 (25 mL) was treated with tetrahydrothiophene (1.20 g, 13.6 mmol) drop-wise over 5 min at RT under nitrogen with stirring. The reaction mixture was then refluxed under nitrogen at 45 °C for 1 d. The CH_2Cl_2 was removed under vacuum and anhydrous diethyl ether (20 mL) was added to the resulting residue and it was stirred for 1 h to precipitate the product 1-(2-bromoethyl)tetrahydro-1*H*-thiophenium trifluoromethanesulfonate **12**, which was isolated by filtration as a white solid (3.00 g, 66%) and was used in the next step without further purification.

A suspension of **12** (4.70 g, 13.6 mmol) and silver (I) oxide (6.30 g, 27.2 mmol) in deionized water (10 mL) and THF (10 mL) was stirred for 20 h at RT. Then the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), dried over $MgSO_4$, filtered, evaporated and the residue was again dissolved in CH_2Cl_2 (10 mL) and passed through silica. The residue was washed with CH_2Cl_2 (200 mL) and then with 10% MeOH in CH_2Cl_2. The solvent was removed under vacuum and the desired product **11** was isolated as a clear oil (2.00 g, 56%); R_f 0.16 (MeOH-DCM, 1:10); δ_H (400 MHz; $CDCl_3$) 6.73 (1 H, dd, *J* 16.5, 9.0, CH_2=C*H*), 6.44 (1 H, dd, *J* 16.5, 2.5, *H*HC=CH), 6.35 (1 H, dd, *J* 9.0, 2.5, *H*HC=CH), 3.94 (2 H, m, SCH*H*), 3.54 (2 H, m, SC*H*H), 2.46 (4 H, m, $SCH_2CH_2CH_2$); δ_c (100 MHz; $CDCl_3$) 135.3 (d), 124.3 (t), 47.2 (t), 28.9 (t); ν_{max}(neat)/cm^{-1} 1450, 1426, 1256, 1165, 1030; *m/z* (CI^+) 115 (M–OTf^-); HRMS (CI^+) $C_6H_{11}S$ requires: 115.0581; found 115.0581.

Use of primary amines, carbamates and amides as substrates

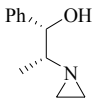
Treatment of norephedrine with vinyl sulfonium salt in the presence of DBU afforded aziridine **13** (Scheme 1). In 2003 Mukaiyama reported similar chemistry, where aziridines were obtained by treating primary amines with vinyl sulfonium salts.[18] When NaH was used a highly polar product resulted which was difficult to isolate (Scheme 1). Use of carbamate and amide substrates did not lead to any cyclization with a range of bases (Scheme 2).



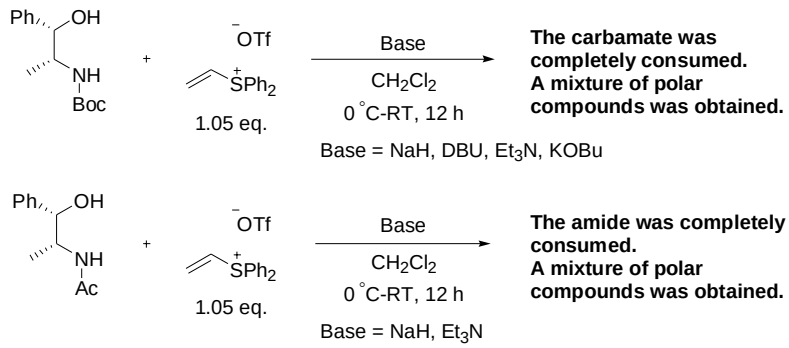
Base	Aziridine	
DBU	52%	
NaH	0%	(Highly polar product resulted)

Scheme 1: Reaction of vinyl sulfonium salt 1 with primary amines.

(1*S*,2*R*)-2-Aziridin-1-yl-1-phenylpropan-1-ol 13[19]

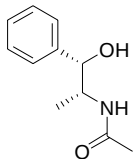


Following general method **B**, using D-(+)-norephedrine (0.050 g, 0.33 mmol), DBU (0.100 g, 0.657 mmol) and diphenylvinylsulfonium salt **1** (0.140 g, 0.386 mmol), after chromatography (CH_2Cl_2-MeOH-NH_3, 89:1:10) the title compound **13** was isolated as a colorless gummy solid (0.030 g, 51%); δ_H (400 MHz; $CDCl_3$) 7.30-7.20 (5 H, m, ArH), 4.79 (1 H, d, *J* 3.5, PhCH), 3.24 (1 H, s, OH), 1.74-1.70 (1 H, m, NCH*H*), 1.67-1.62 (1 H, m, NCH*H*), 1.39 (1 H, qd, *J* 6.5, 3.5, MeCH), 1.17-1.12 (2 H, m, NC*HH*), 0.90 (3 H, d, *J* 6.5, CH_3); δ_C (100.5 MHz, $CDCl_3$) 141.4 (s), 128.1 (d), 127.1 (d), 126.1 (d), 75.5 (d), 71.5 (d), 27.7 (t), 26.2 (t), 13.3 (q); ν_{max}(neat)/cm^{-1} 2927, 1451, 1259; HRMS (CI^+) $C_{11}H_{16}NO$ requires: 178.1232; found 178.1230.



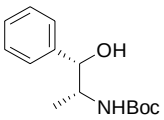
Scheme 2: Reaction of vinyl sulfonium salt 1 with carbamate and amide substrates.

N-[(1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]acetamide 14[20]



The D-(+)-norephedrine (1.00 g, 6.61 mmol) was dissolved into 1 M NaOH (7.25 mL) solution, stirred at 0 °C for 5 min and then acetyl chloride (0.617 g, 7.86 mmol) was added dropwise. The reaction mixture was further stirred for 2 h at RT. The required product was precipitated out and it was separated by filtration, washed with water, dried under high vacuum, the target compound **14** was obtained as a colorless solid (1.08 g, 85%); R_f 0.15 (EtOAc-PE, 6:4); δ_H (400MHz; $CDCl_3$) 7.36-7.23 (5 H, m, ArH), 5.54-5.51 (1 H, m), 4.82 (1 H, d, *J* 3.0, C*H*OH), 4.38-4.29 (1 H, m, NCH), 3.6 (1 H, br s, OH), 2.01 (3 H, s, $COCH_3$), 0.99 (3 H, d, *J* 6.5); δ_C (100 MHz, $CDCl_3$) 171.0 (s), 140.7 (s), 128.2 (d), 127.6 (d), 126.3 (d), 76.5 (d), 51.1 (d), 23.3 (q), 14.5 (q).

tert-Butyl [(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]carbamate 15[21,22]



According to the procedure reported by Wieland and co-workers,[21] to a suspension of D-(+)-norephedrine (1.00 g, 6.61 mmol) in dimethylformamide (5 mL) was added triethylamine (1.33 g, 13.1 mmol) and the reaction mixture was stirred under argon for 30 min. Then di-*tert*-butyl dicarbonate (1.50 g, 6.87 mmol) in DMF (5 mL) was added and the reaction mixture was stirred overnight at RT. The DMF was removed under high vacuum, and the resulting residue was dissolved in ethyl acetate (50 mL) and was

added water (35 mL). The aqueous layer was extracted twice with ethyl acetate (10mL), and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum and the title compound **15** was isolated as white solid (1.30 g, 78%); mp 86-88 °C (Et_2O) [lit.[22] mp 88-89 °C (Et_2O-hexane)]; δ_H (400 MHz; $CDCl_3$) 7.31 (5 H, m, ArH), 4.86 (1 H, br dd, *J* 4.0, 3.5, PhCH), 4.62 (1 H, br s), 4.10-3.99 (1 H, m, NCH), 3.25 (1 H, br s), 1.47 (9 H, s, $C(CH_3)_3$), 0.99 (3 H, d, *J* 7.0, CH_3CH); δ_C (100 MHz, $CDCl_3$) 156.5 (s), 140.8 (s), 128.2 (d), 127.5 (d), 126.4 (d), 79.9 (s), 76.9 (d), 52.0 (d), 28.4 (q), 14.9 (q).

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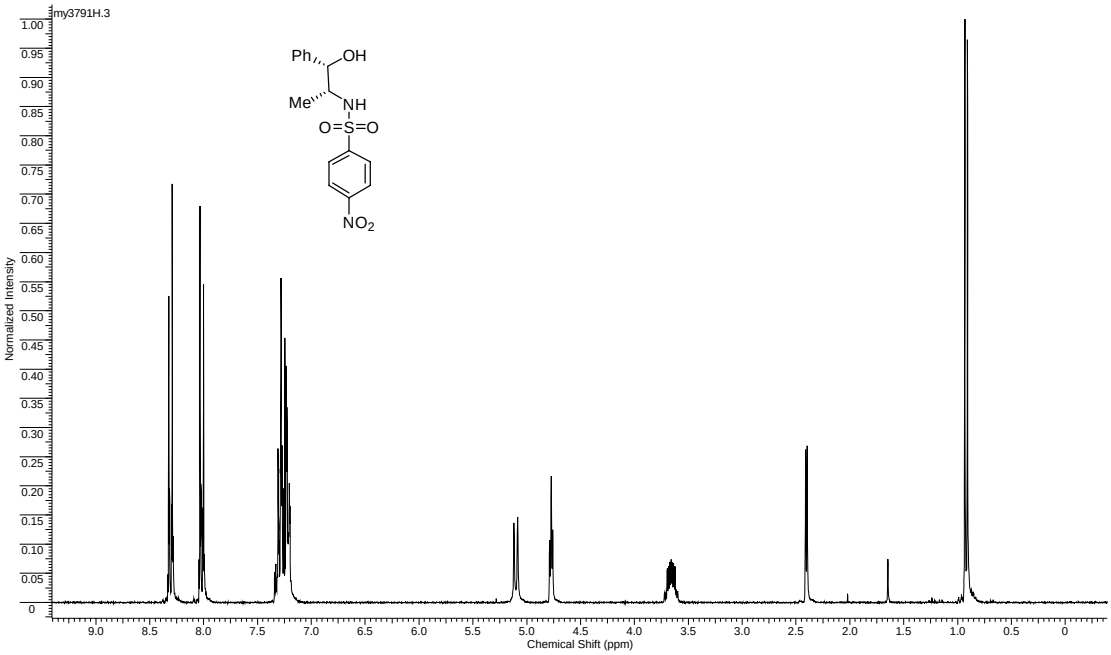
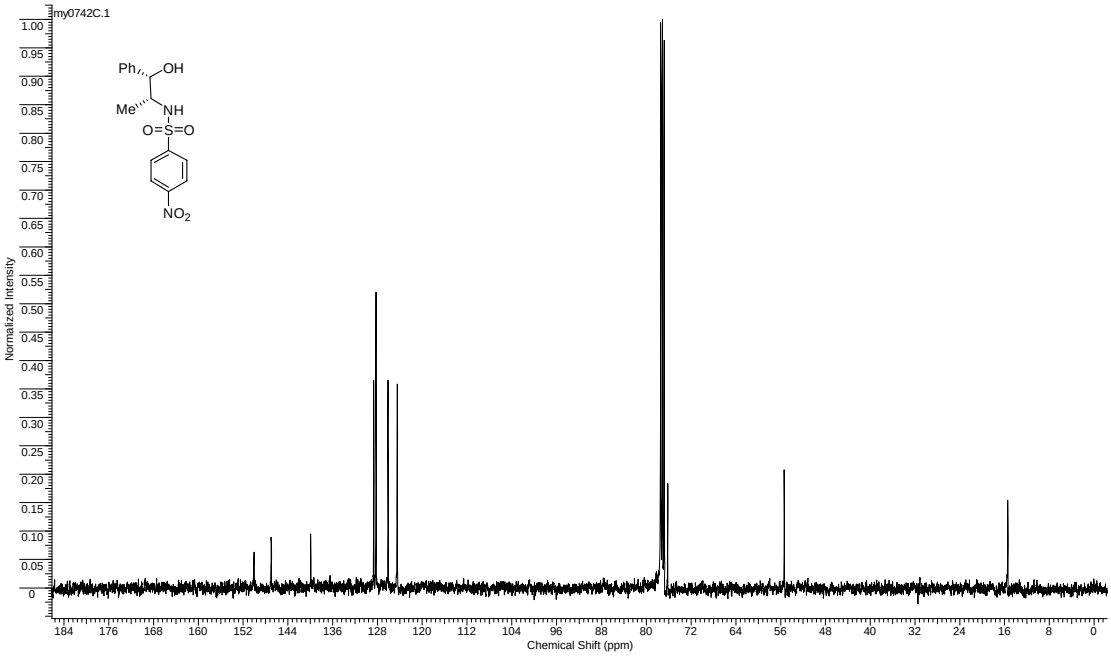
NMR Spectrum of sulfonamide 2f

[(1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-4-nitrobenzenesulfonamide 2f

^{1}H NMR (400 MHz), $CDCl_3$



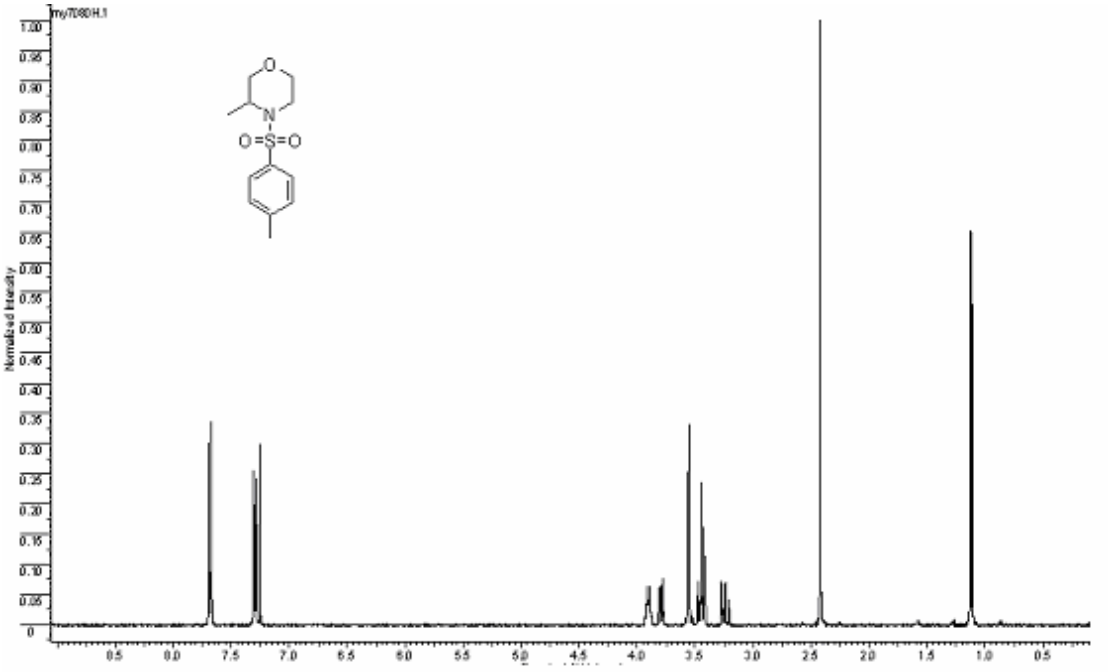
^{13}C NMR (100 MHz), $CDCl_3$



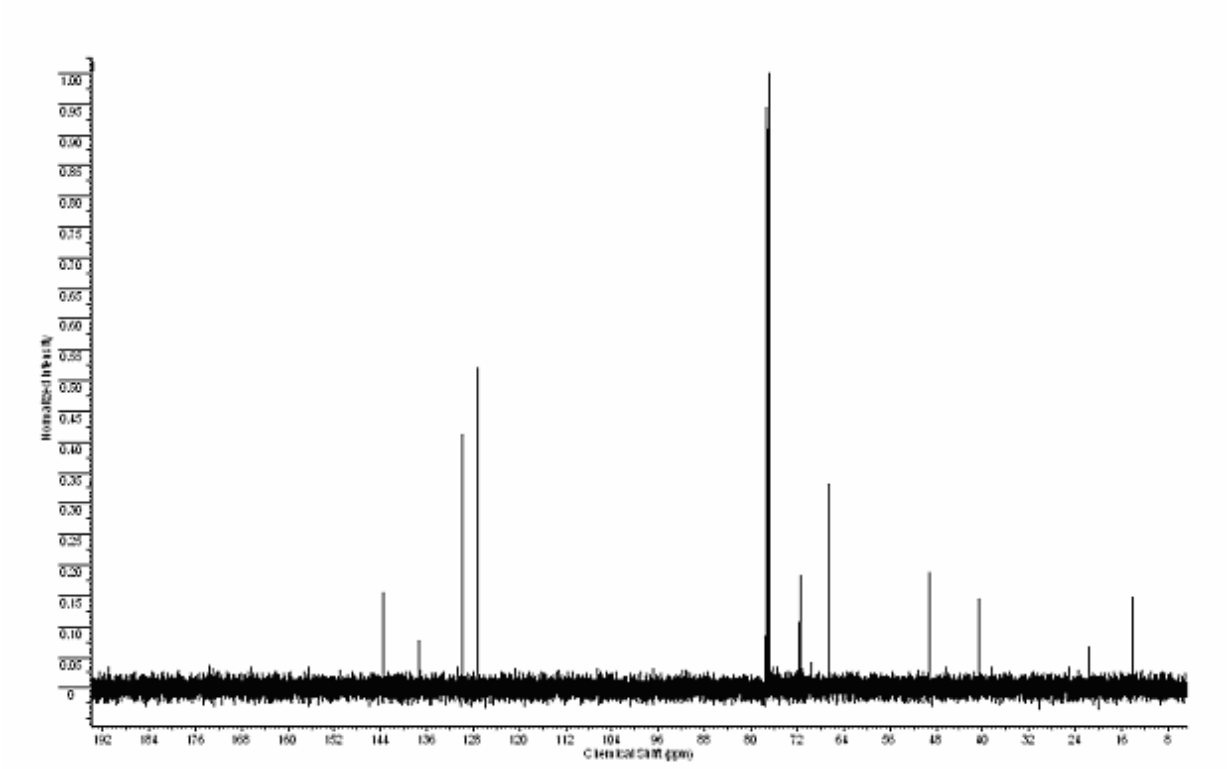
NMR Spectra of morpholines 3a-3f

(±)-3-Methyl-4-[(4-methylphenyl)sulfonyl]morpholine 3a

^{1}H NMR (400 MHz), $CDCl_3$

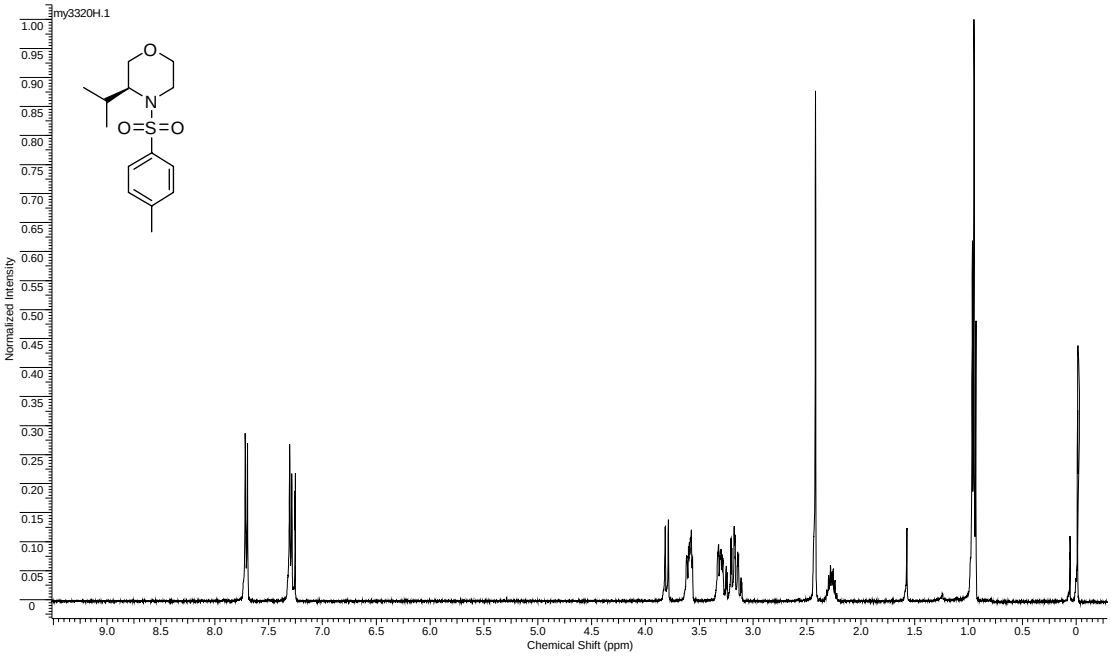


^{13}C NMR (100 MHz), $CDCl_3$

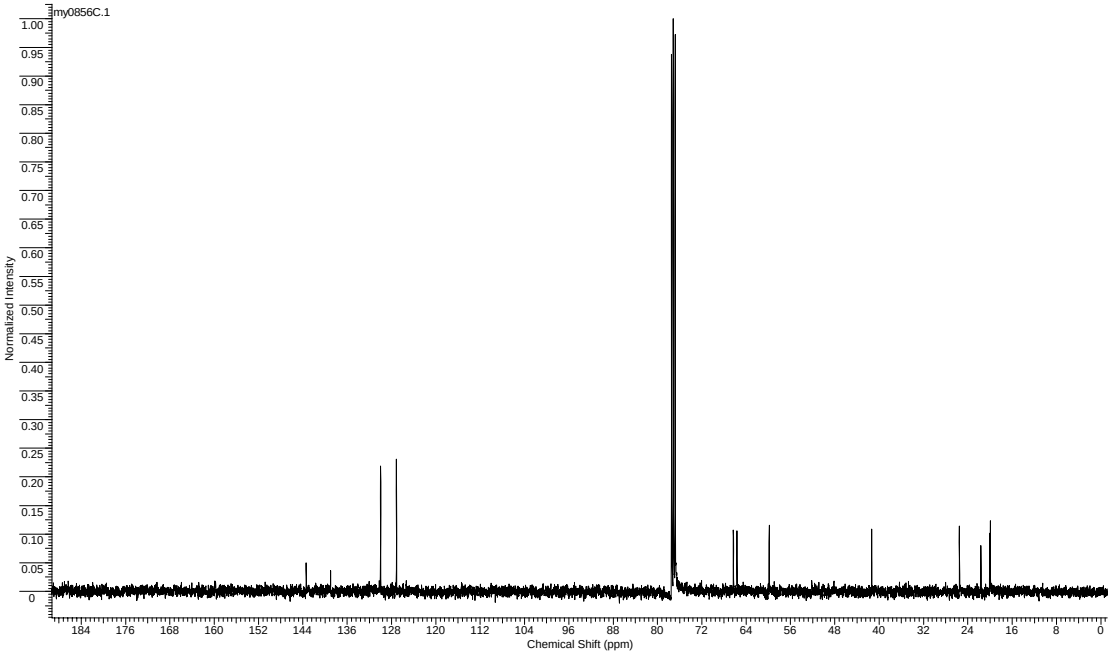


(3*S*)-3-Isopropyl-4-[(4-methylphenyl)sulfonyl]morpholine 3b

^{1}H NMR (400 MHz), $CDCl_3$

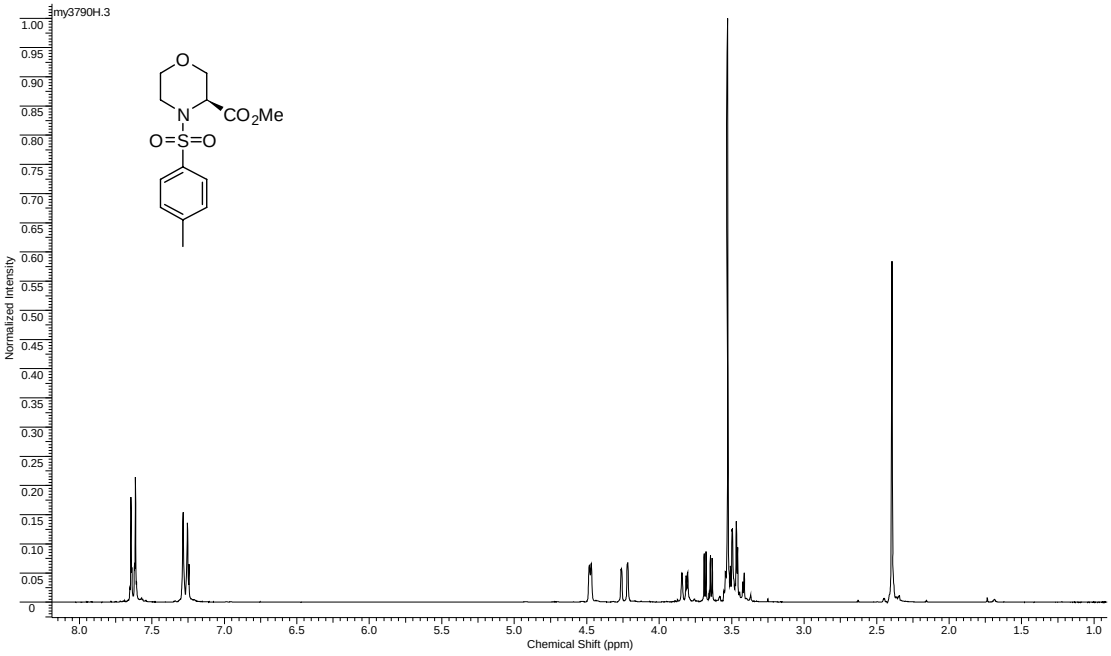


^{13}C NMR (100 MHz), $CDCl_3$

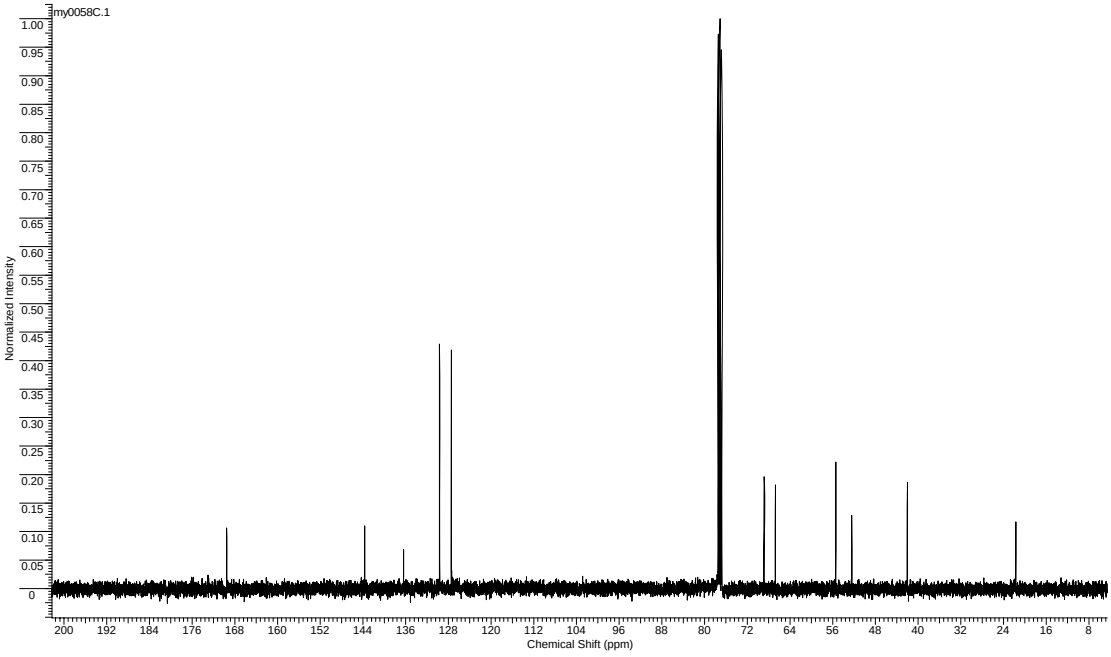


Methyl (3*S*)-4-[(4-methylphenyl)sulfonyl]morpholine-3-carboxylate 3c

^{1}H NMR (400 MHz), $CDCl_3$

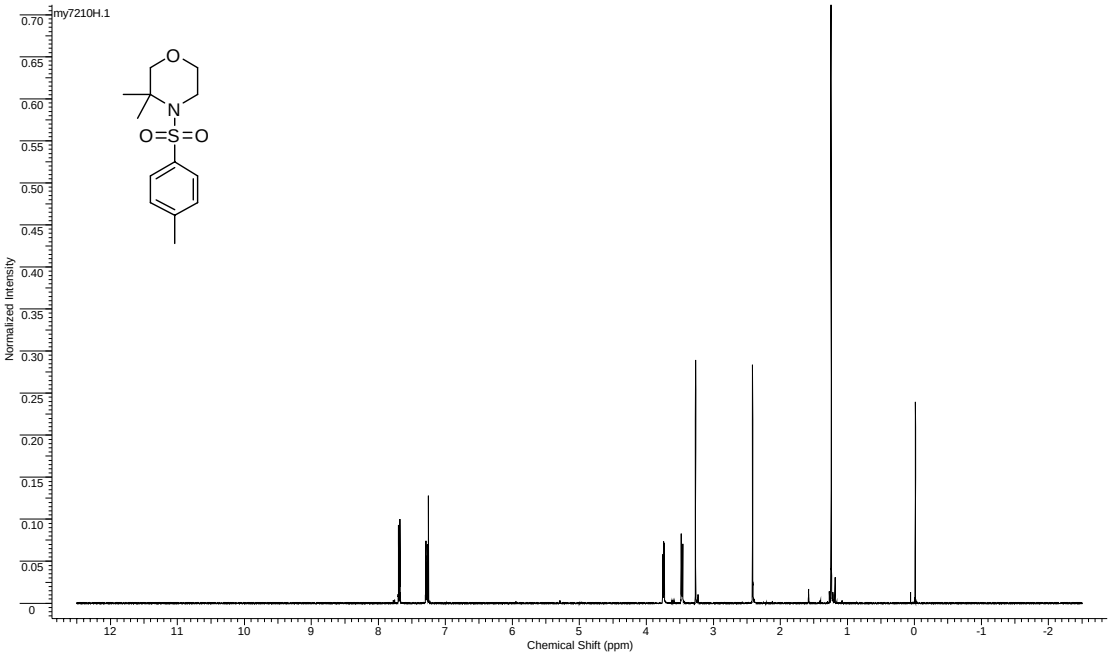


^{13}C NMR (100 MHz), $CDCl_3$

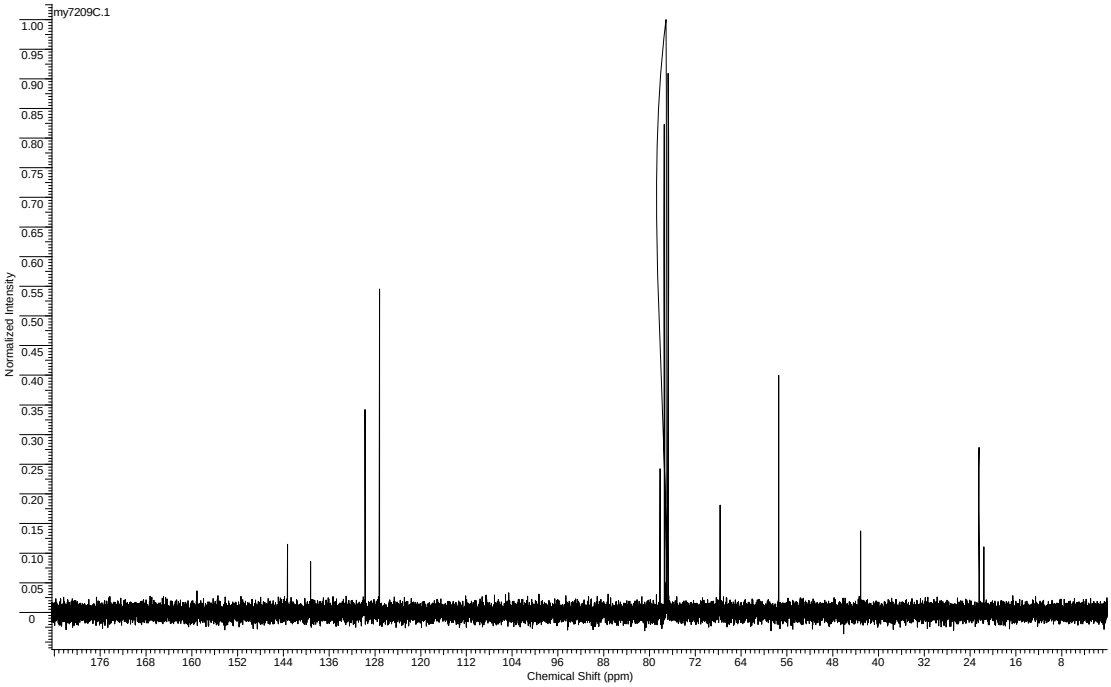


3,3-Dimethyl-4-[(4-methylphenyl)sulfonyl]morpholine 3d

^{1}H NMR (400 MHz), $CDCl_3$

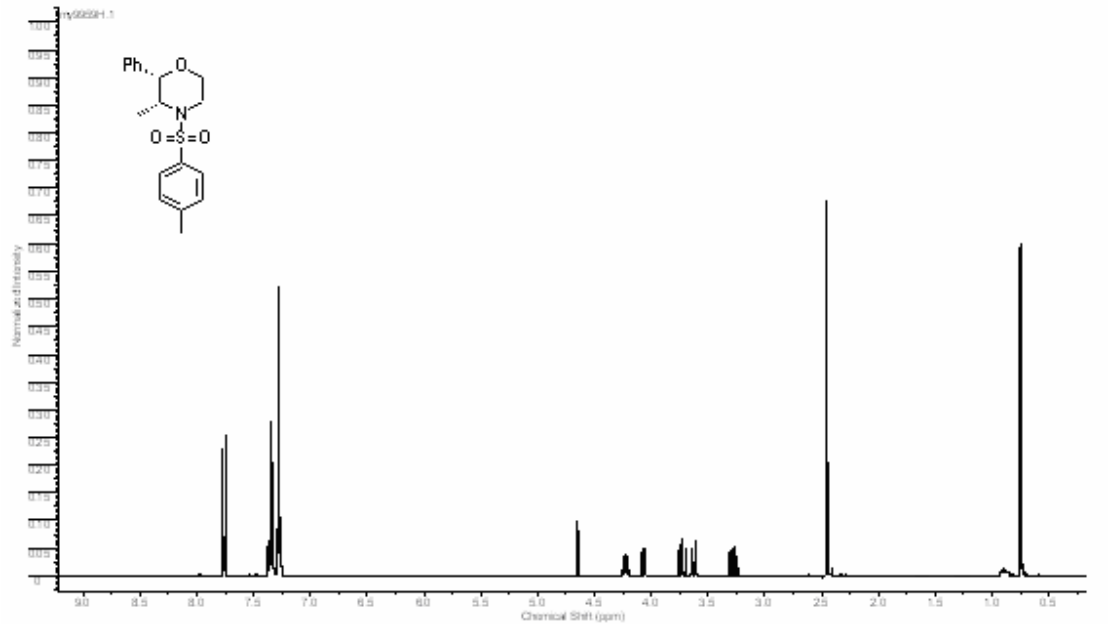


^{13}C NMR (100 MHz), $CDCl_3$

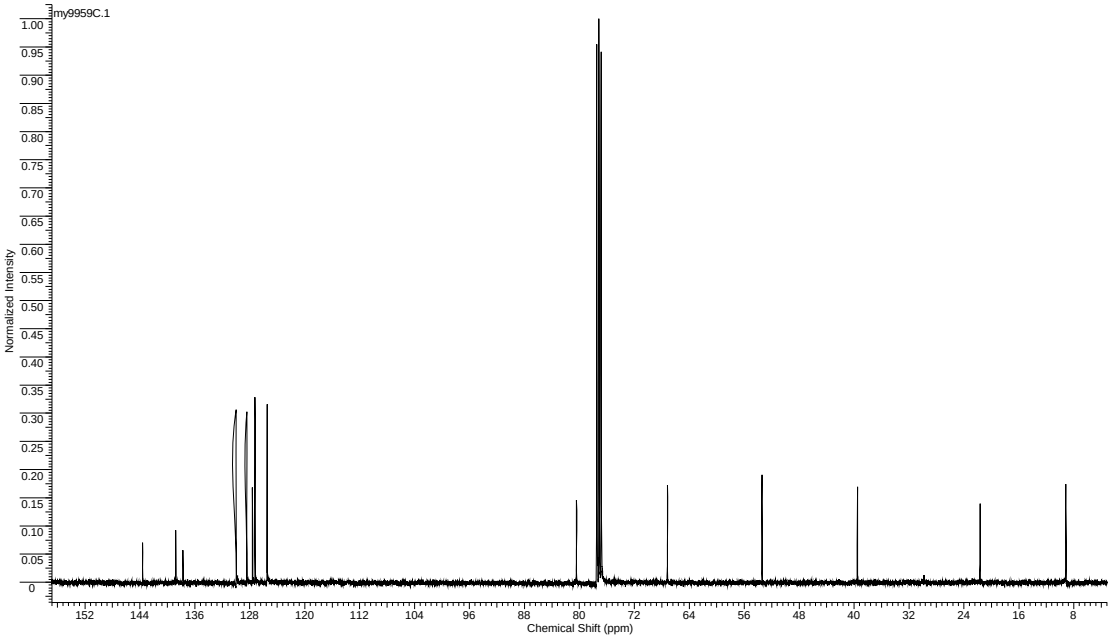


(2*S*,3*R*)-3-Methyl-4-[(4-methylphenyl)sulfonyl]-2-phenylmorpholine 3e

^{1}H NMR (400 MHz), $CDCl_3$

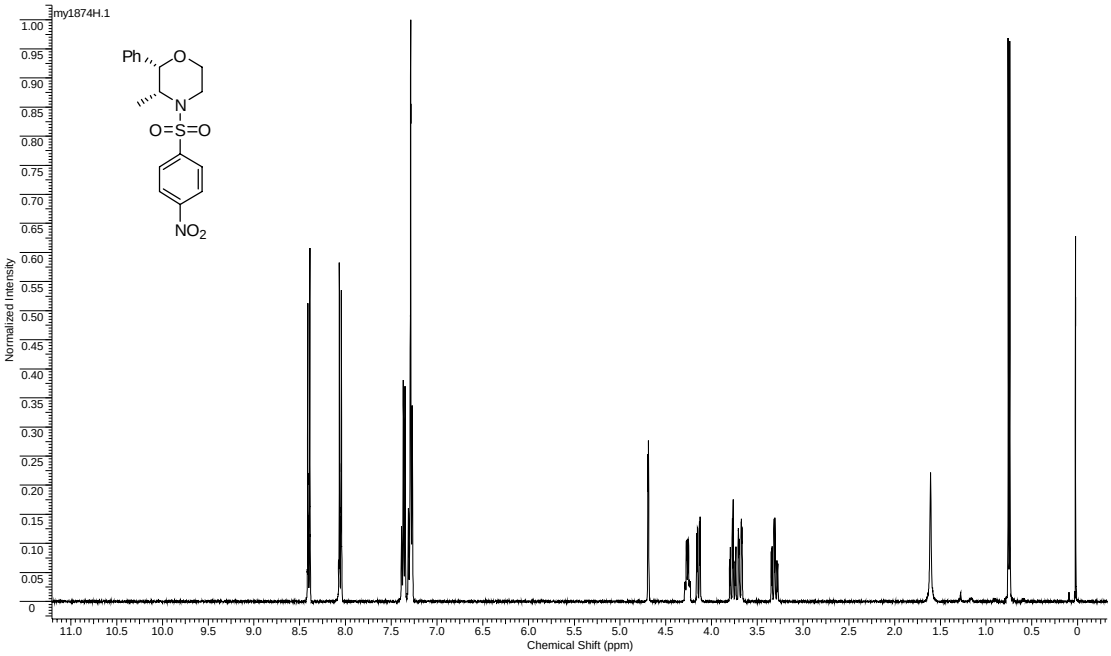


^{13}C NMR (100 MHz), $CDCl_3$

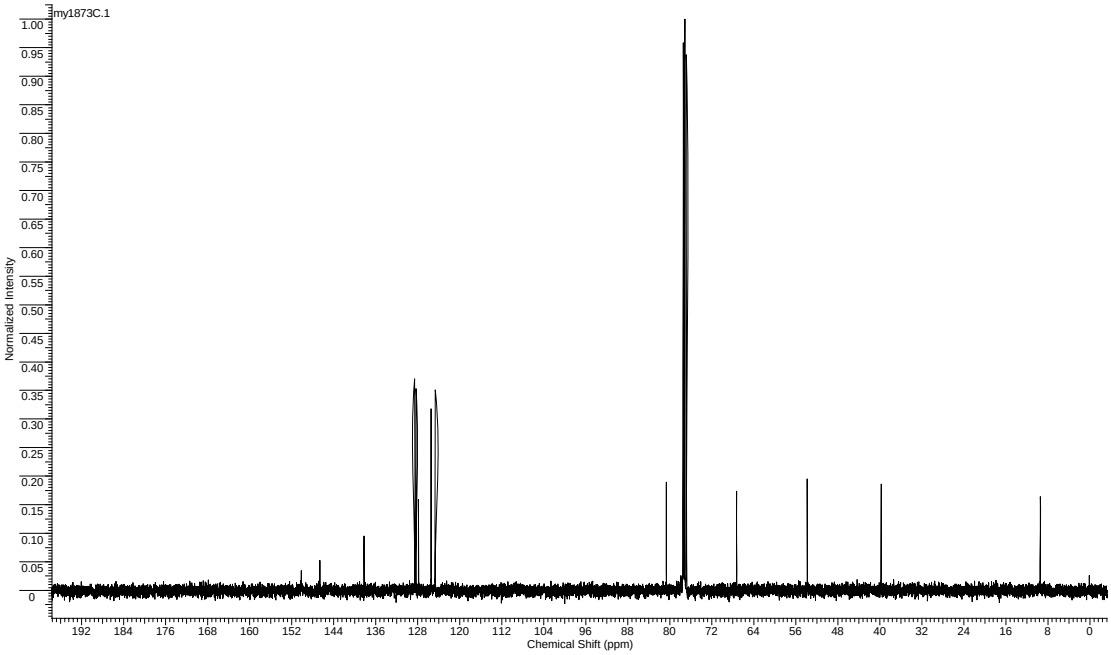


(2*S*,3*R*)-3-Methyl-4-[(4-nitrophenyl)sulfonyl]-2-phenylmorpholine 3f

^{1}H NMR (400 MHz), $CDCl_3$



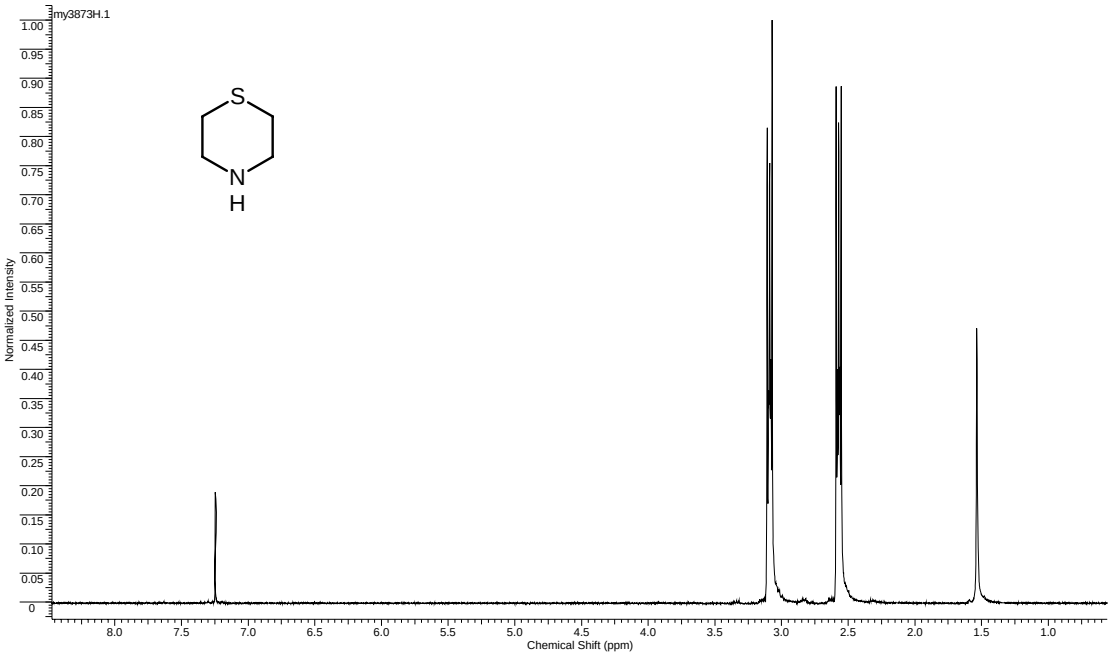
^{13}C NMR (100 MHz), $CDCl_3$



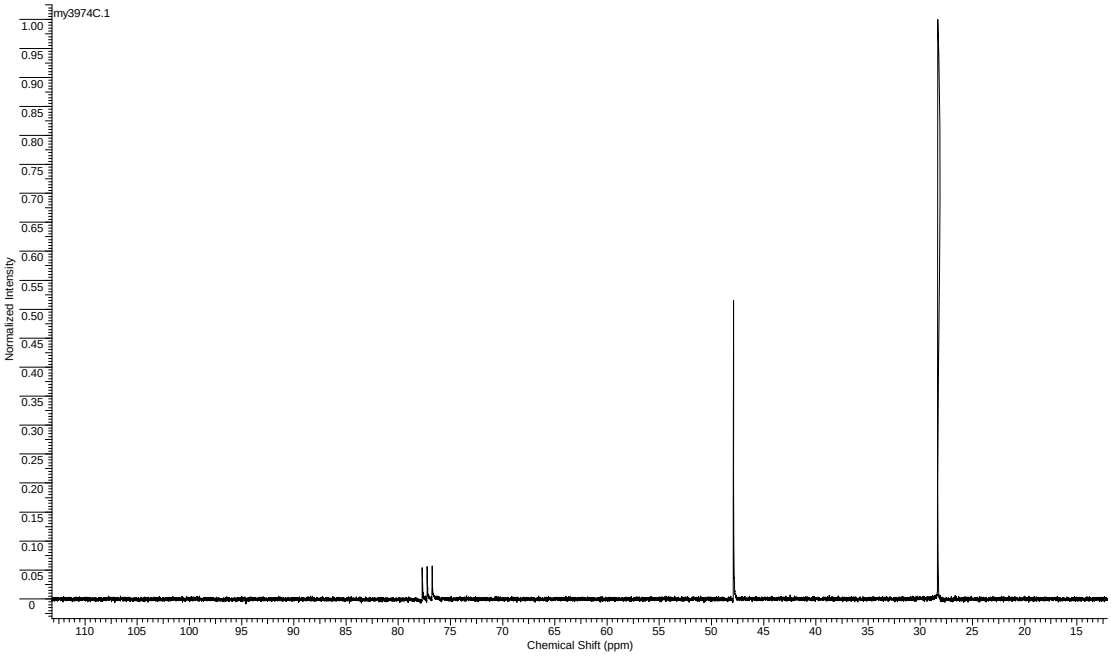
NMR Spectra of thiomorpholines 3g, 8, 3i

Thiomorpholine 3g

^{1}H NMR (270 MHz), $CDCl_3$

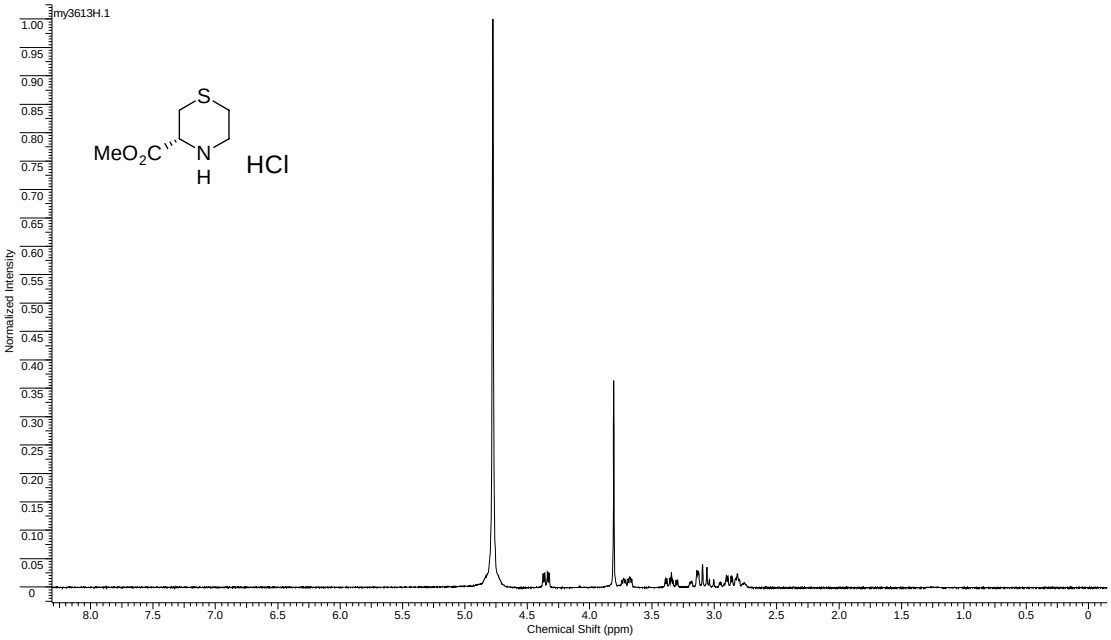


^{13}C NMR (100 MHz), $CDCl_3$

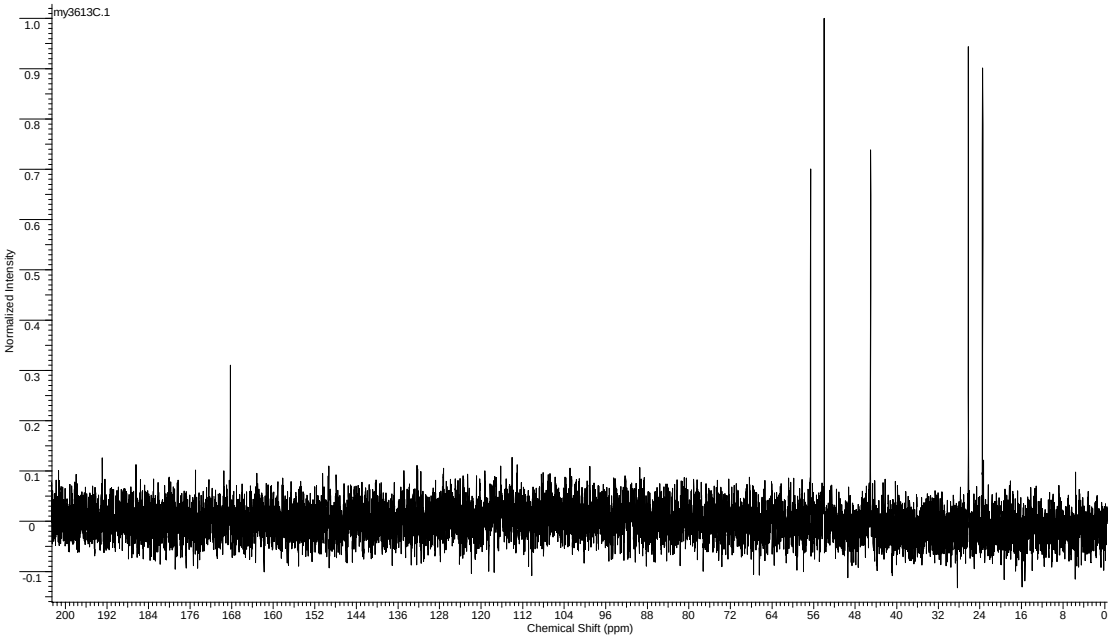


Thiomorpholine-(3*R*)-carboxylic acid methyl ester hydrochloride 8

^{1}H NMR (270 MHz), D_2O

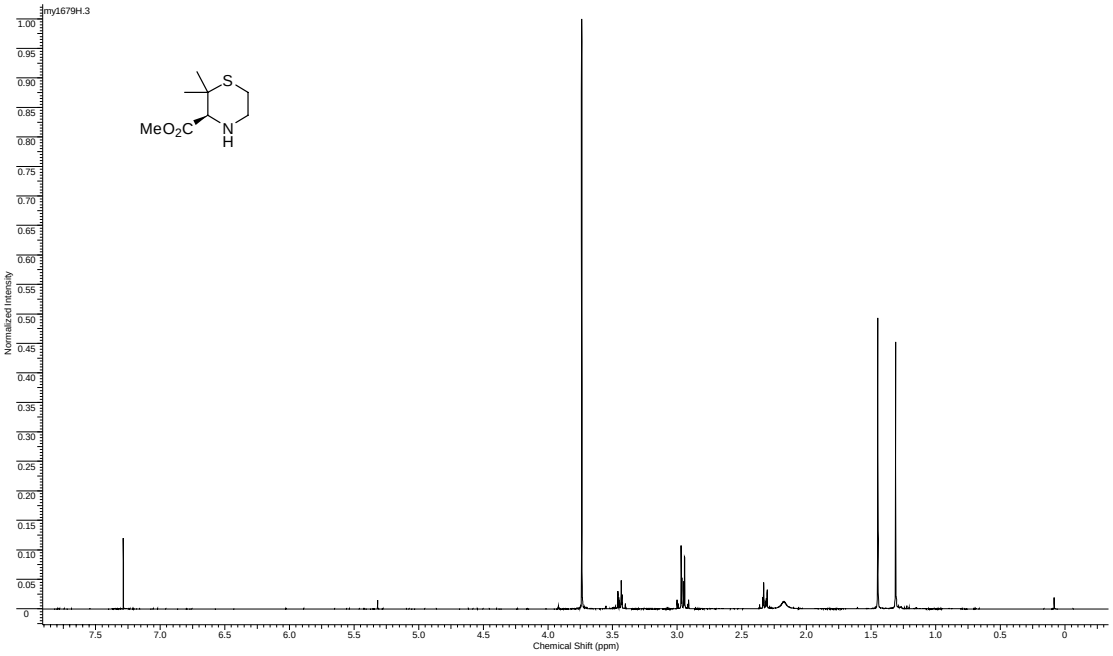


^{13}C NMR (100 MHz), D_2O

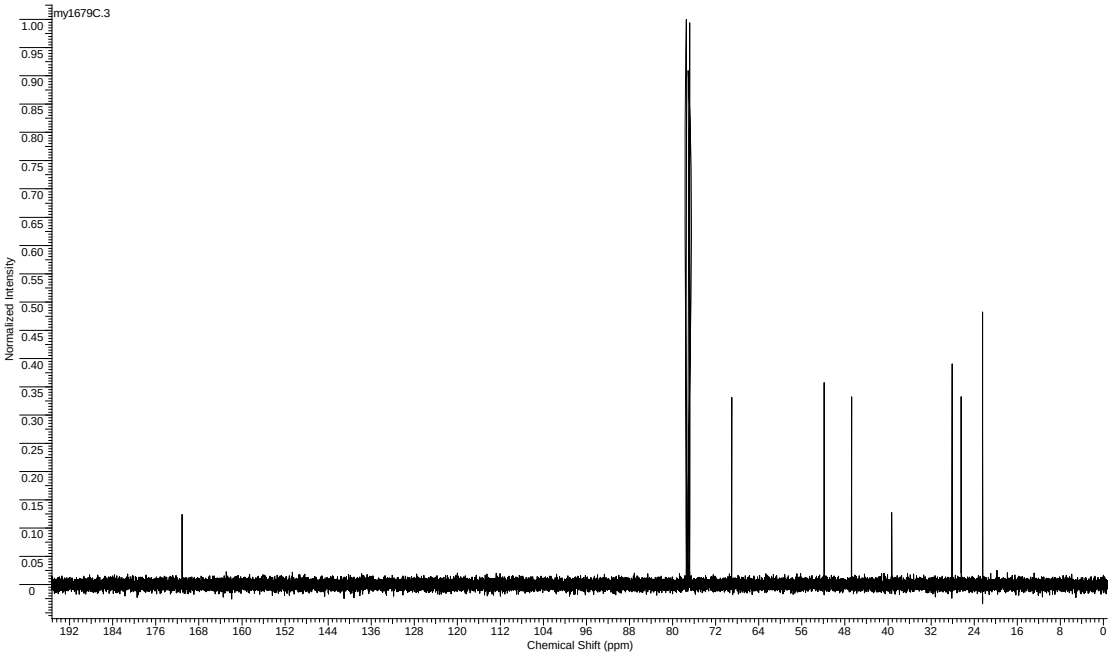


Methyl (3*S*)-2,2-dimethylthiomorpholine-3-carboxylate 3i

^{1}H NMR (400 MHz), $CDCl_3$



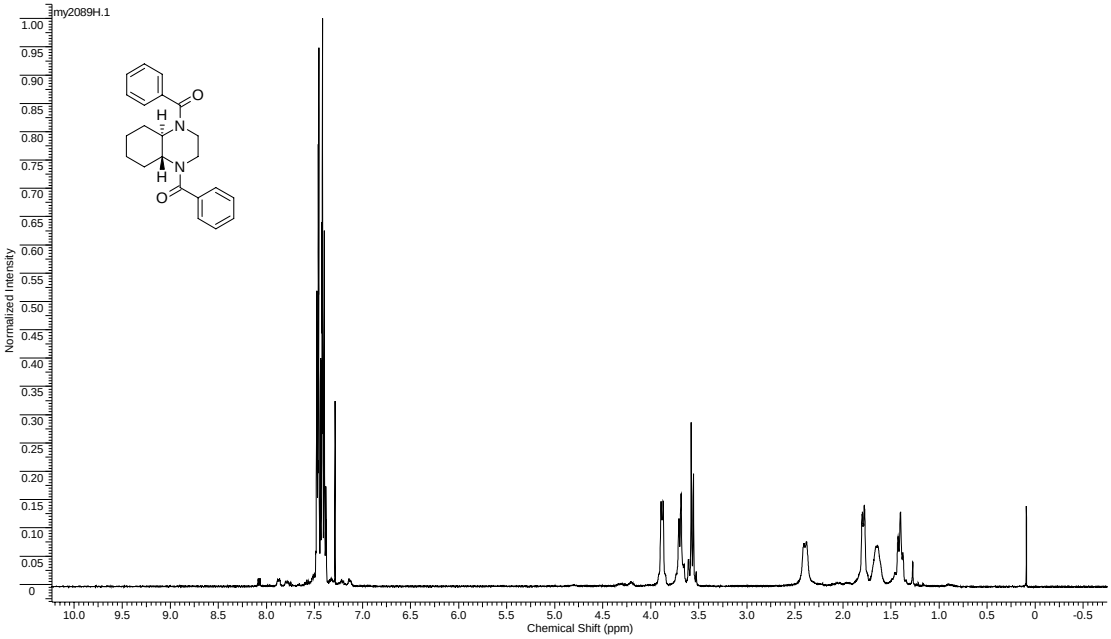
^{13}C NMR (100 MHz), $CDCl_3$



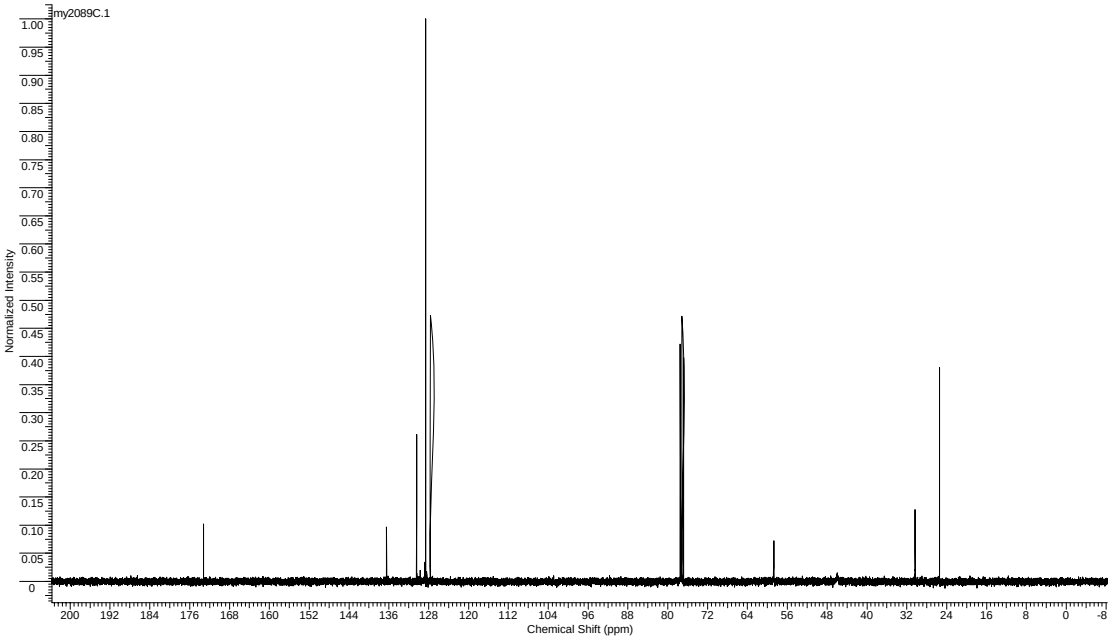
NMR Spectra of piperazines 3j-3m

(±)-1,4-Dibenzoyldecahydroquinoxaline 3j

^{1}H NMR (400 MHz), $CDCl_3$

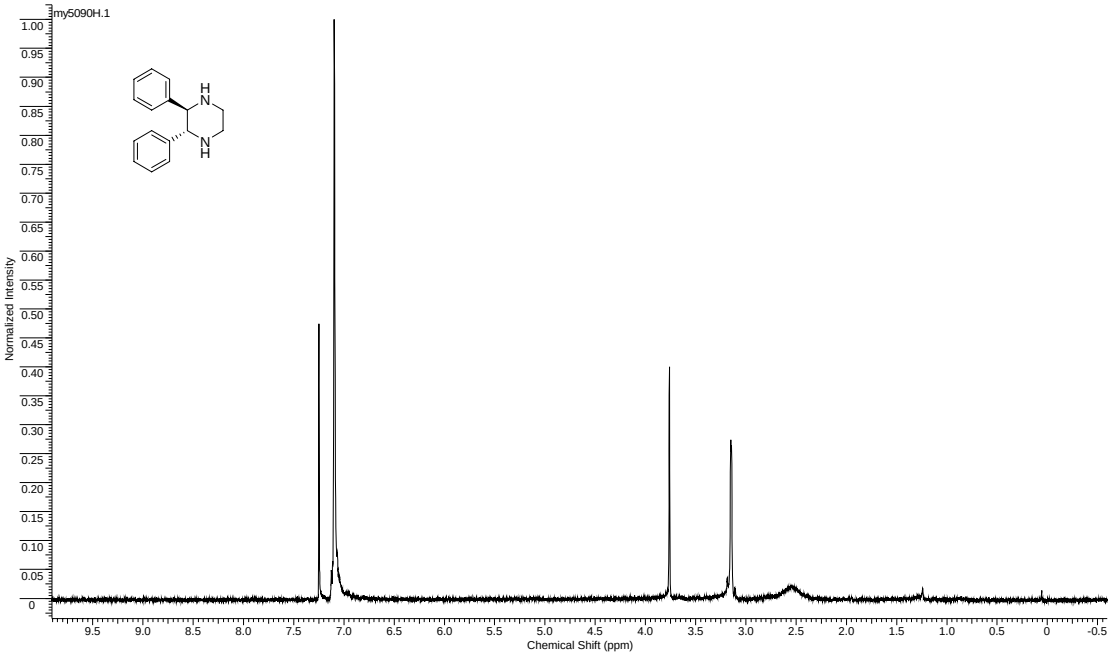


^{13}C NMR (100 MHz), $CDCl_3$

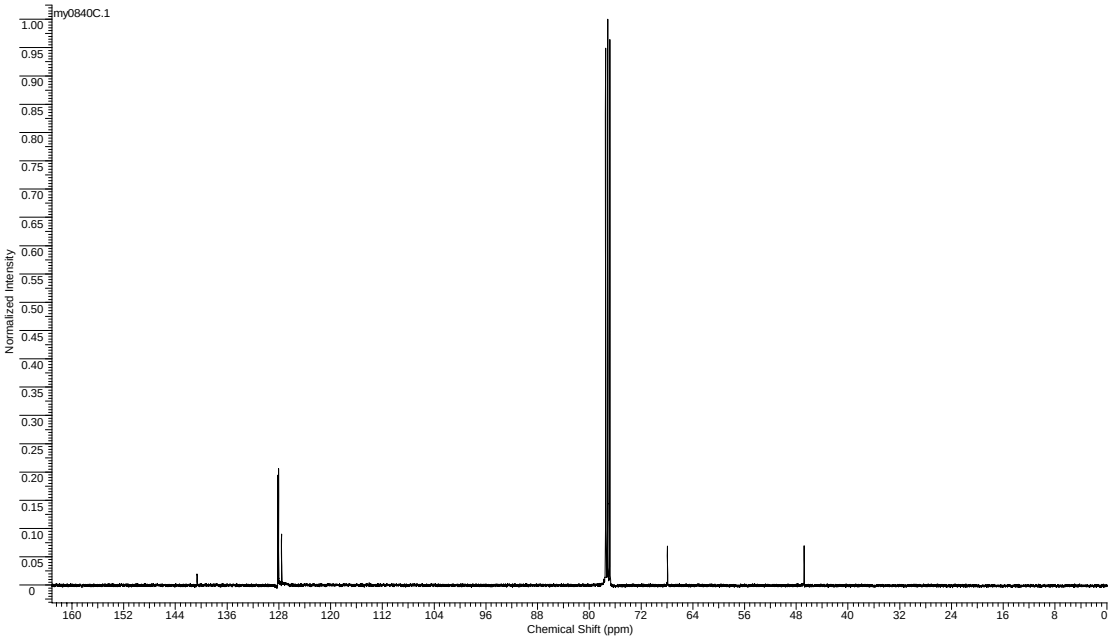


(2*R*,3*R*)-Diphenylpiperazine 3k

^{1}H NMR (400 MHz), $CDCl_3$

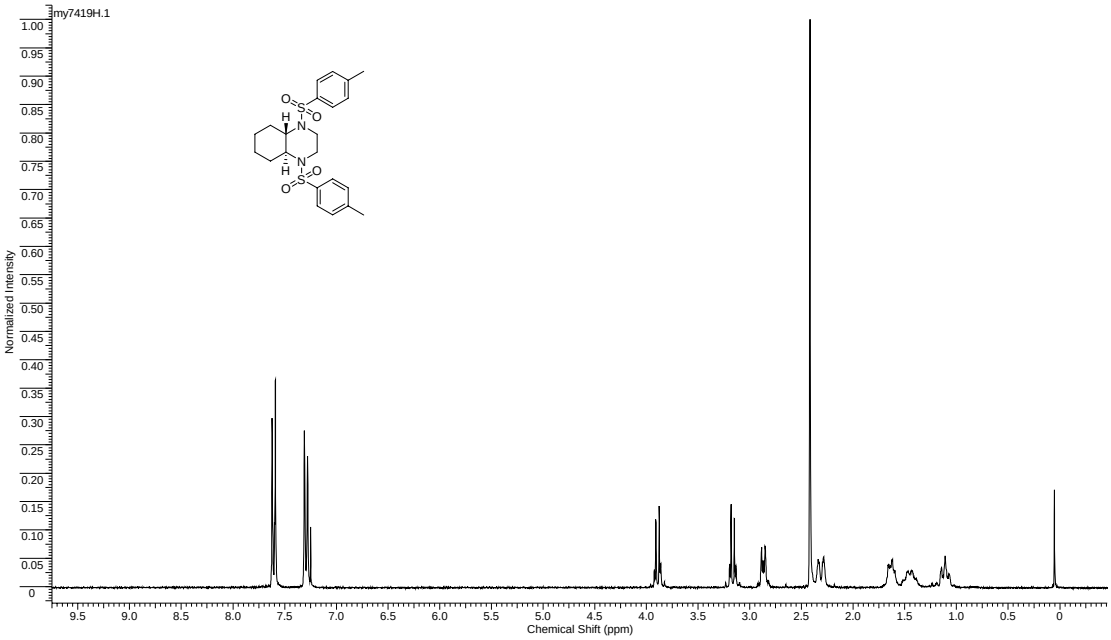


^{13}C NMR (100 MHz), $CDCl_3$

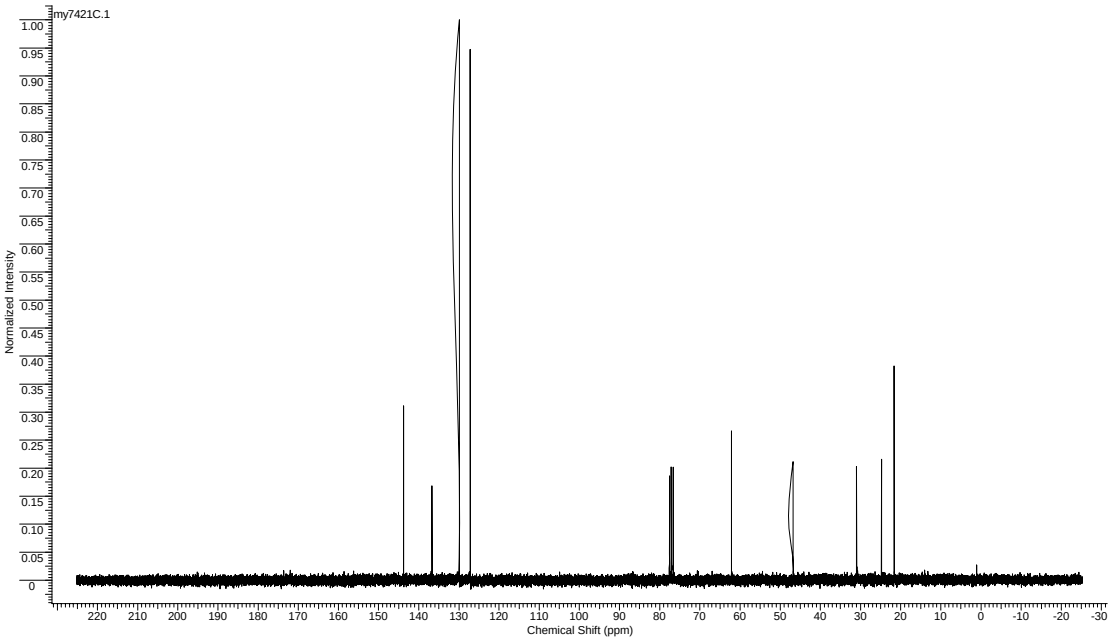


(±)-1,4-Bis(toluene-4-sulfonyl)decahydroquinoxaline 3l

^{1}H NMR (400 MHz), $CDCl_3$

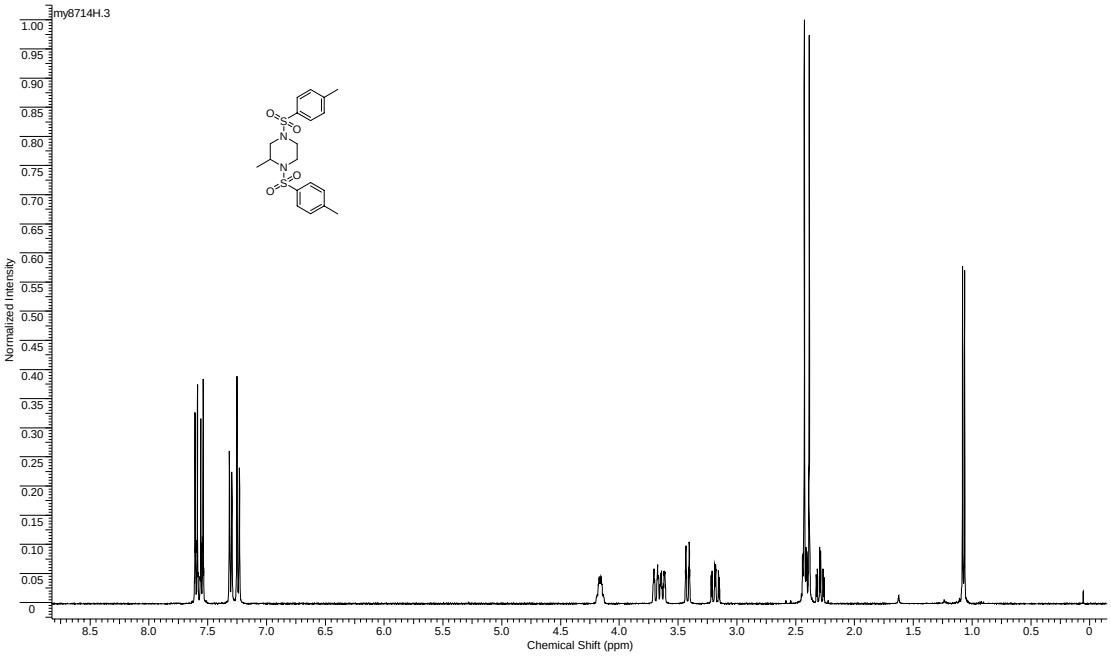


^{13}C NMR (100 MHz), $CDCl_3$

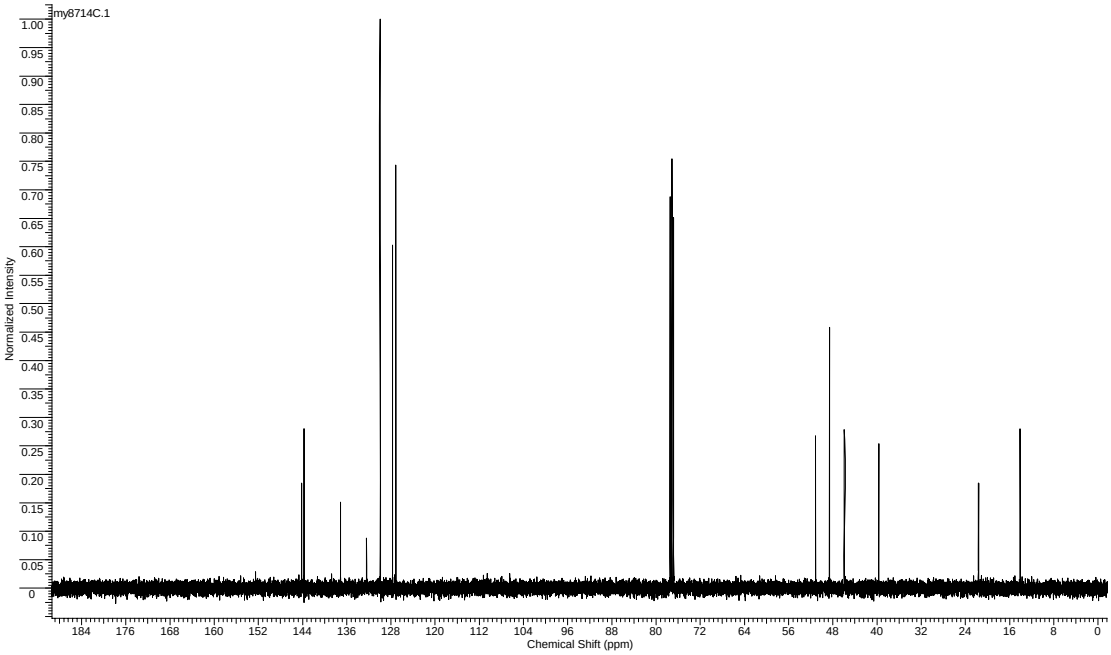


(±)-2-Methyl-1,4-ditosylpiperazine 3m

^{1}H NMR (400 MHz), $CDCl_3$



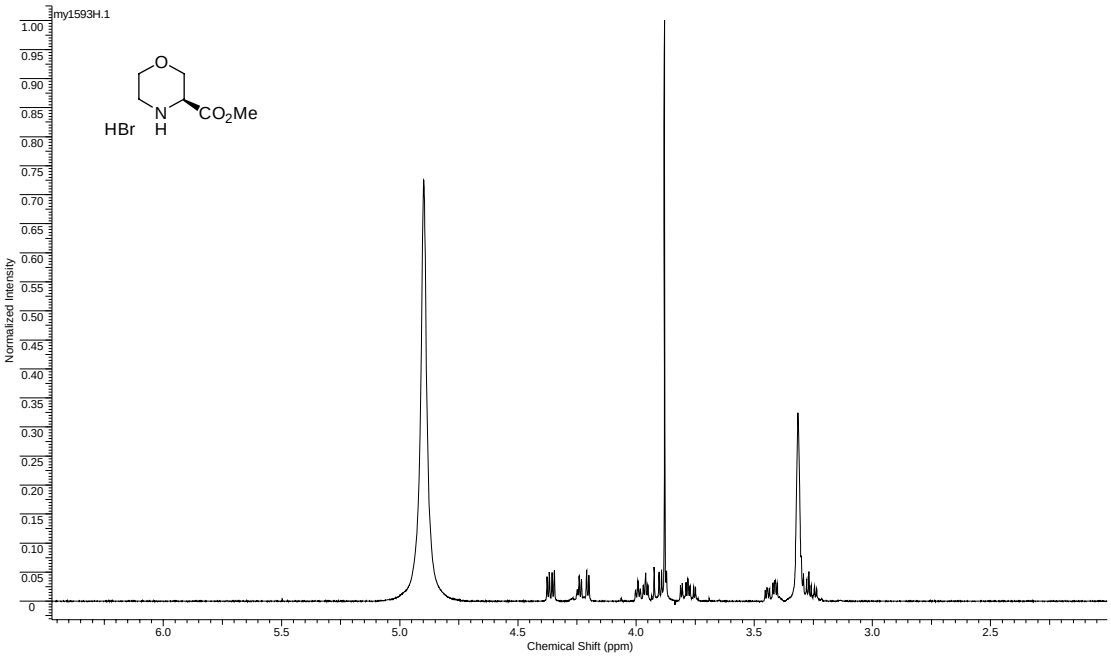
^{13}C NMR (100 MHz), $CDCl_3$



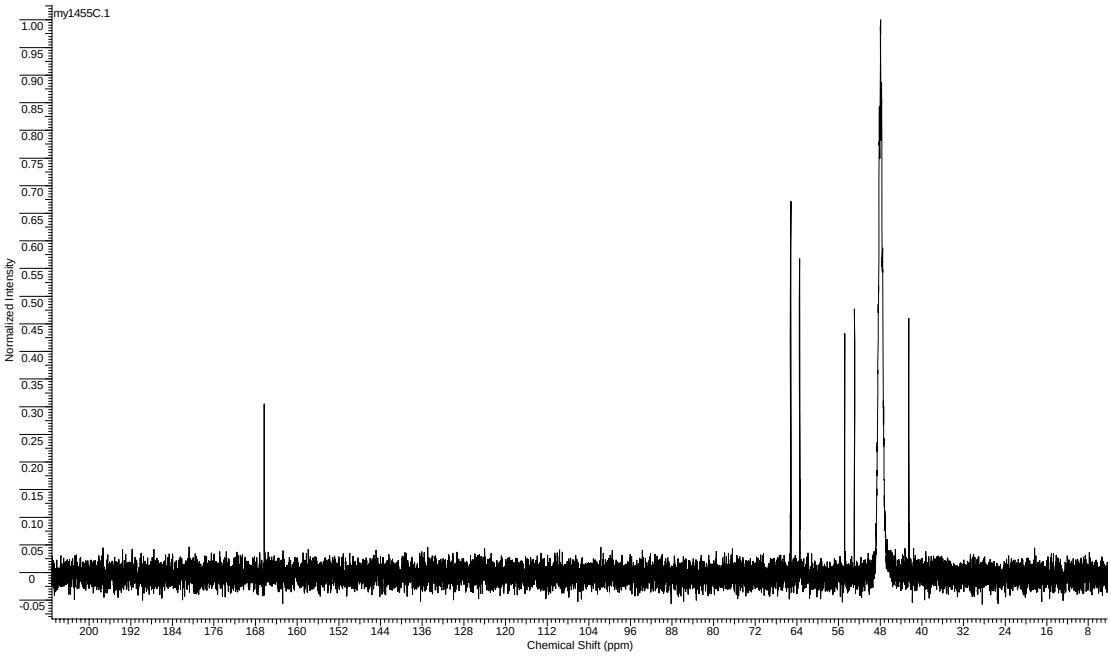
NMR Spectra of morpholines 9, 10, 6

Methyl (3*S*)-morpholine-3-carboxylate hydrobromide 9

^{1}H NMR (400 MHz), CD_3OD

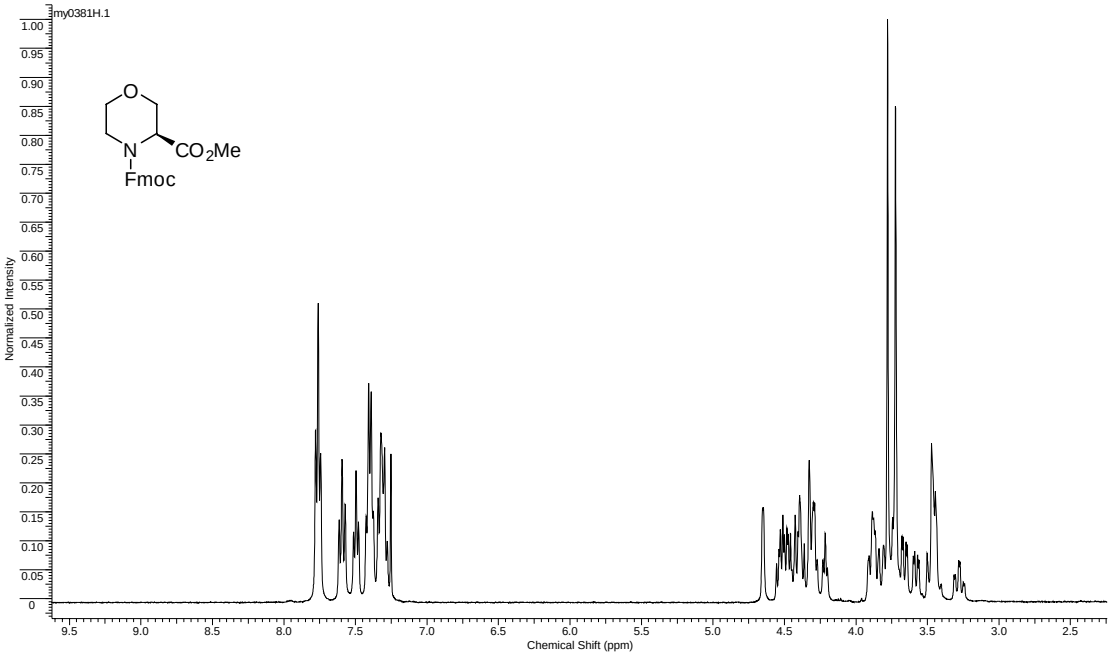


^{13}C NMR (100 MHz), CD_3OD

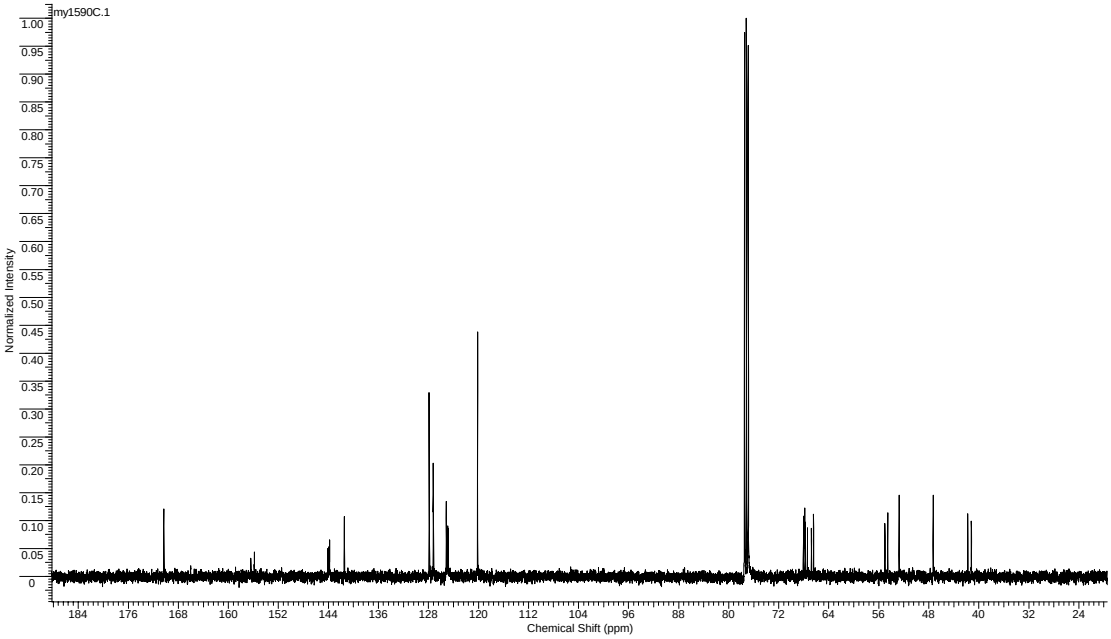


4-(9*H*-Fluoren-9-ylmethyl) 3-methyl (*S*)-morpholine-3,4-dicarboxylate 10

^{1}H NMR (400 MHz), $CDCl_3$

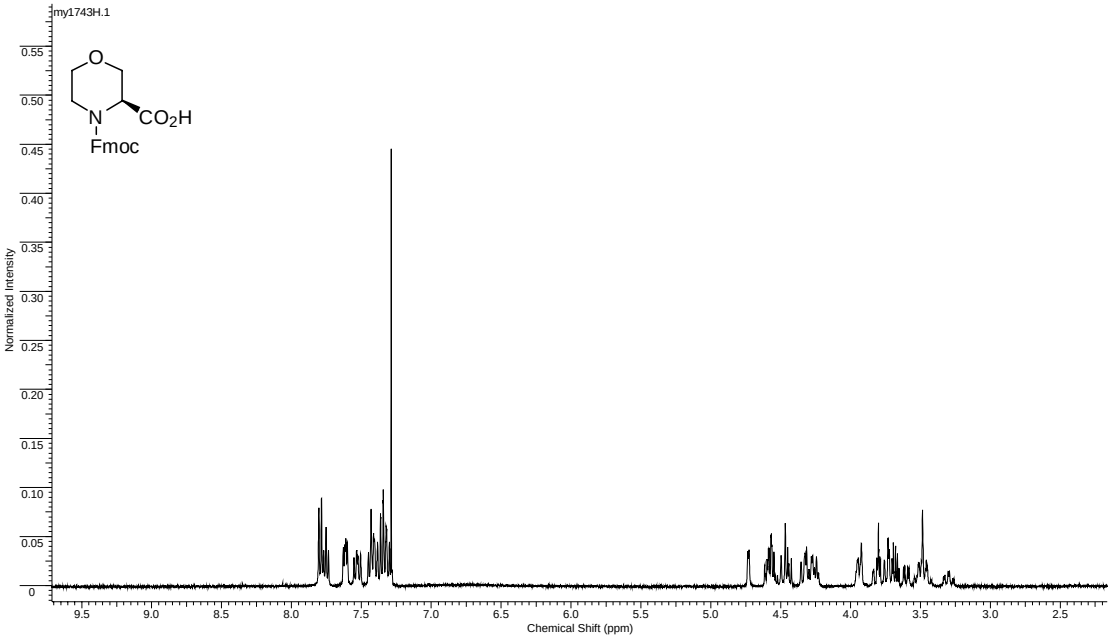


^{13}C NMR (100 MHz), $CDCl_3$

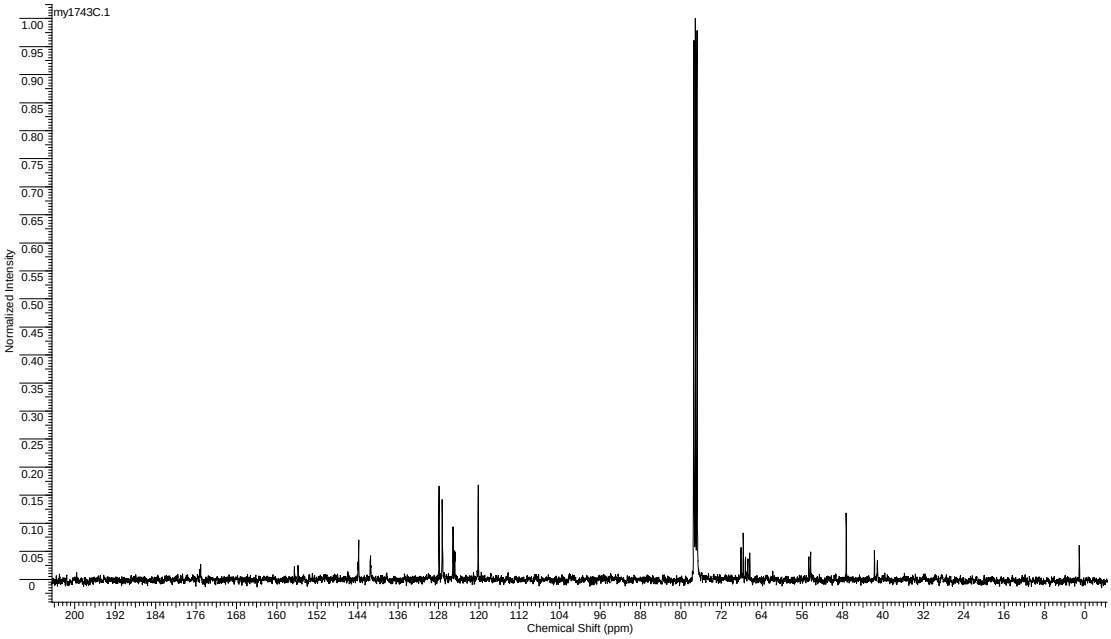


(3*S*) 4-[(9*H*-Fluoren-9-ylmethoxy)carbonyl] morpholine-3-carboxylic acid 6

^{1}H NMR (400 MHz), $CDCl_3$



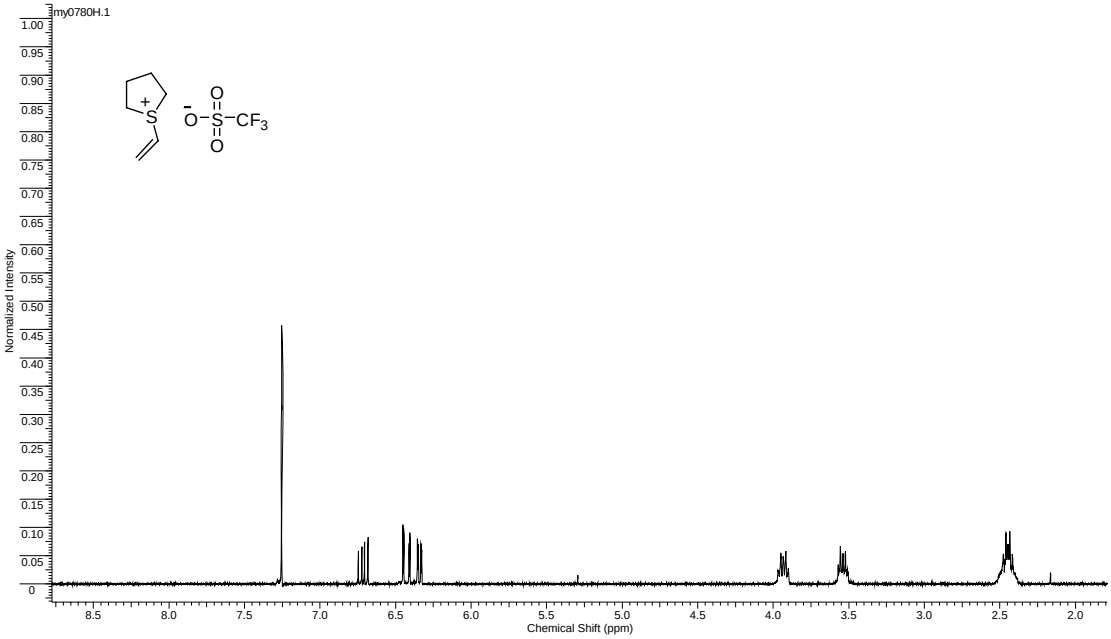
^{13}C NMR (100 MHz), $CDCl_3$



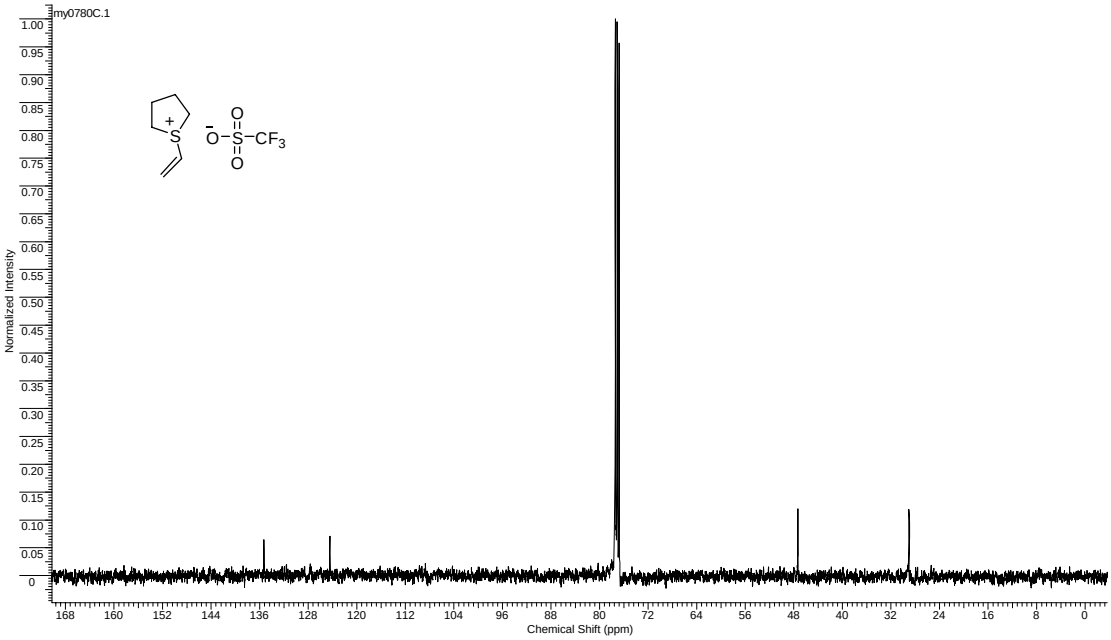
NMR Spectrum of vinyl sulfonium salt 11

1-Vinyltetrahydro-1*H*-thiophenium trifluoromethanesulfonate 11

^{1}H NMR (400 MHz), $CDCl_3$



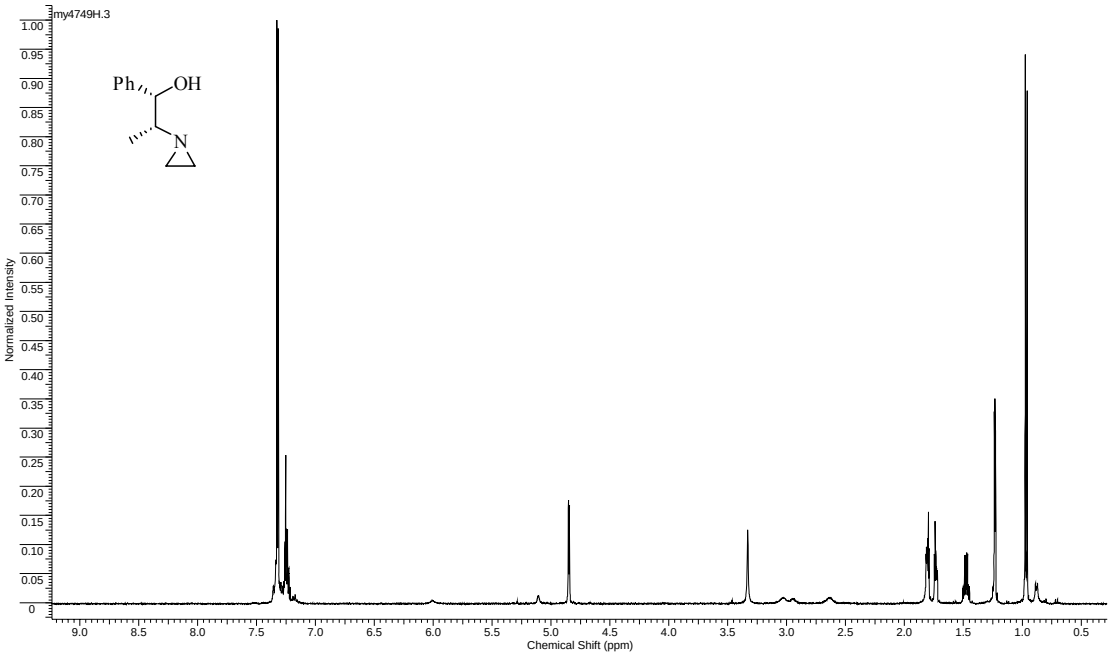
^{13}C NMR (100 MHz), $CDCl_3$



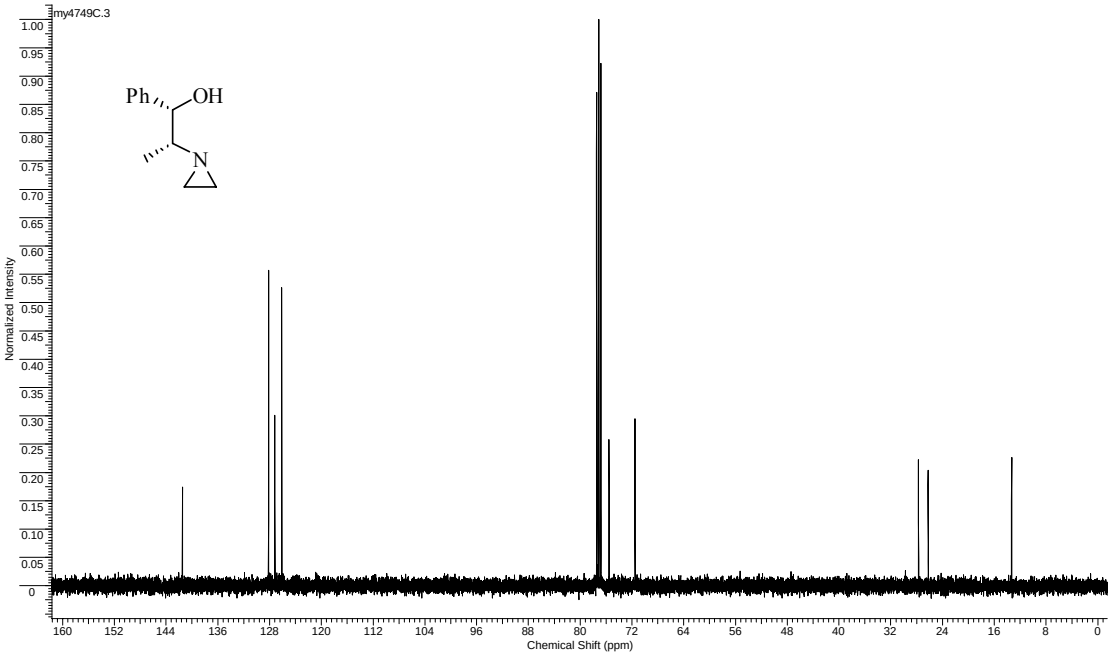
NMR Spectra of D-(+)-norephedrine derivatives 13, 14 and 15

(1*S*,2*R*)-2-Aziridin-1-yl-1-phenylpropan-1-ol 13

^{1}H NMR (400 MHz), $CDCl_3$

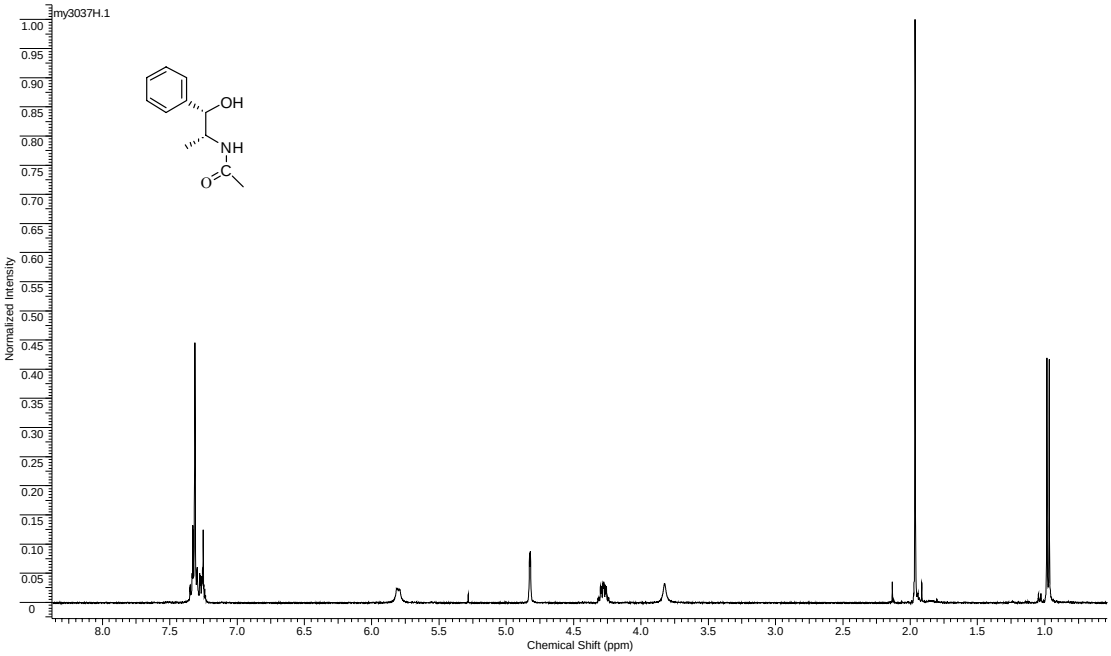


^{13}C NMR (100 MHz), $CDCl_3$

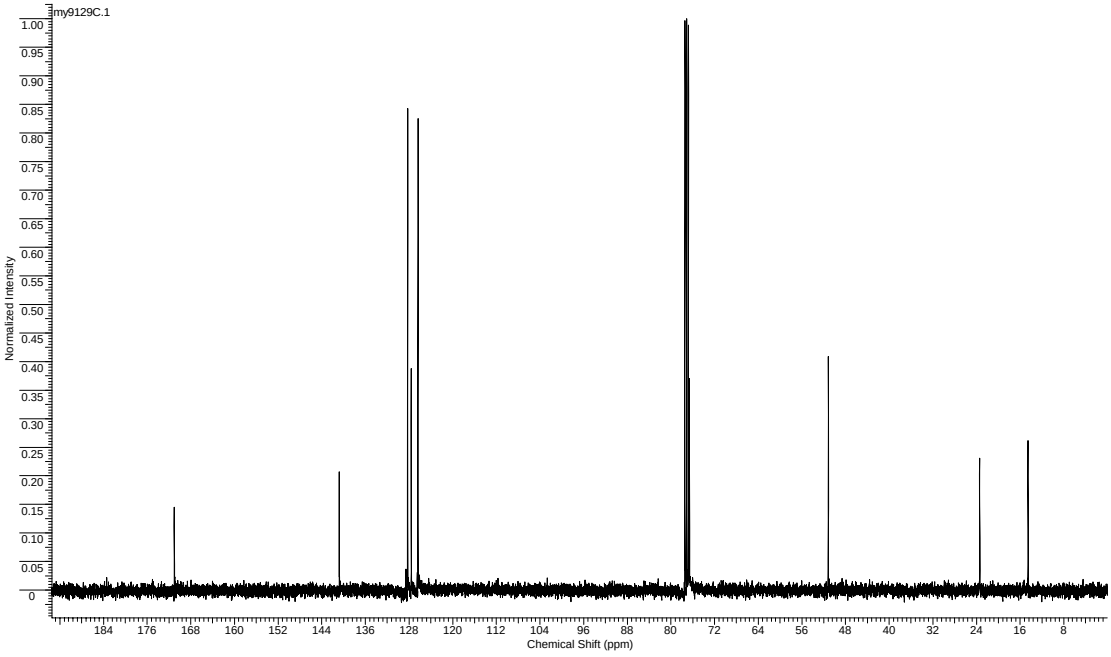


***N*-[(1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]acetamide 14**

^{1}H-NMR (400 MHz), $CDCl_3$

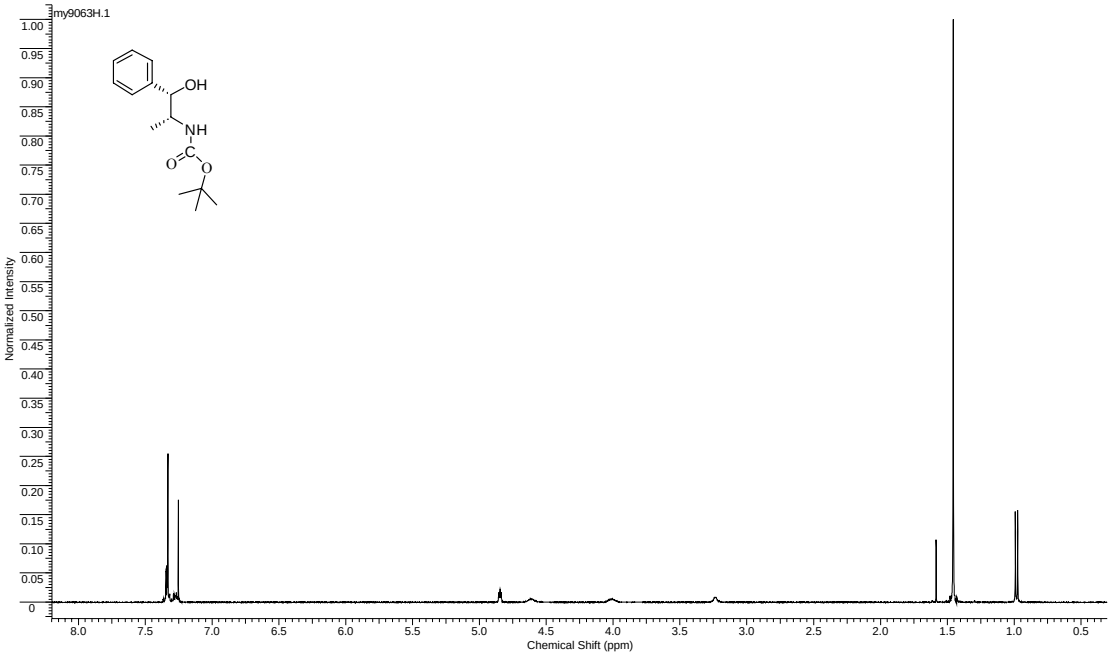


^{13}C-NMR (100 MHz), $CDCl_3$



***tert*-Butyl [(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]carbamate 15**

^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$